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(71) Applicant *(for all designated States except US):* FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* OKADA, Satoshi [JP/JP]; 13-1, Namiki 4-chome, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Kozo [JP/JP]; 1-602-301, Azuma, Tsukuba-shi, Ibaraki 305 (JP). KAYAKIRI, Natsuko [JP/JP]; 2-5-4-506, Umezono, Tsukuba-shi, Ibaraki 305 (JP). SAWADA, Yuki [JP/JP]; 1-602-208, Azuma, Tsukuba-shi, Ibaraki 305 (JP). TANAKA, Hirokazu [JP/JP]; 1-4-8, Ottominami, Tsuchiura-shi, Ibaraki 300 (JP). HASHIMOTO, Masashi [JP/JP]; 2-2-8-1205, Shinmachi, Toride-shi, Ibaraki 302 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

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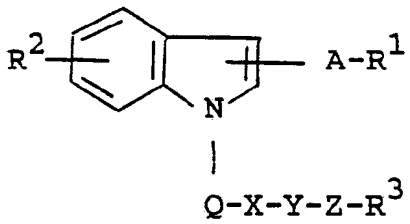
(54) Title: INDOLE DERIVATIVES



(I)

(57) Abstract

Indole derivatives of formula (I), or a salt thereof, which are useful as a testosteron 5α-reductase inhibitor.

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DESCRIPTION

INDOLE DERIVATIVES

The present invention relates to novel indole derivatives and a pharmaceutically acceptable salt thereof. More particularly, it relates to novel indole derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities such as inhibitory activity on testosteron 5α-reductase and the like, to process for preparation thereof, to a pharmaceutical composition comprising the same and to a use of the same as a medicament.

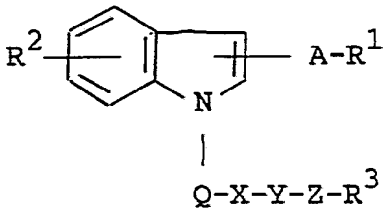
Accordingly, one object of the present invention is to provide novel indole derivatives and a pharmaceutically acceptable salt thereof, which are useful as a testosteron 5α-reductase inhibitor.

Another object of the present invention is to provide process for preparation of said indole derivatives or a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said indole derivatives or a pharmaceutically acceptable salt thereof.

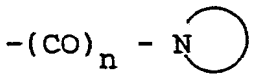
Still further object of the present invention is to provide a use of said indole derivatives or a pharmaceutically acceptable salt thereof as a medicament such as testosteron 5α-reductase inhibitor useful for treating or preventing testosteron 5α-reductase mediated diseases such as alopecia, acnes, prostatism, and the like in human being or animals.

The indole derivatives of the present invention are novel and can be represented by the formula (I) :

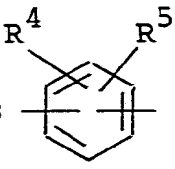
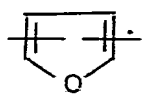


(I)

wherein R^1 is carboxy or protected carboxy,
R^2 is hydrogen, lower alkyl or halogen,
R^3 is aryl or ar(lower)alkyl, each of which may have suitable substituent(s), or a group of the formula :



in which  is heterocyclic group containing nitrogen atom, and
n is 0 or 1,
A is lower alkylene which may be substituted by oxo or lower alkenylene,
Q is carbonyl, sulfonyl or lower alkylene,

X is  or 

in which R^4 is hydrogen or lower alkyl, and
R^5 is hydrogen, lower alkyl or $Y\text{-}Z\text{-}R^3$,

Y is bond or lower alkylene,

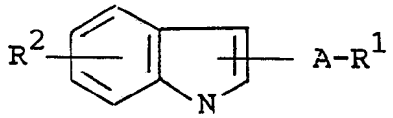
Z is bond, lower alkylene, lower alkenylene, -O-, $-S-$ or $-\overset{R^6}{\underset{|}{N}}-$,

in which R^6 is lower alkyl, ar(lower)alkyl which may have suitable substituent(s) or amino protective group; or

$X-Y-Z-R^3$ is 6H-dibenzo[b,d]pyranyl which may have suitable substituent(s).

According to the present invention, the object compound (I) and a salt thereof can be prepared by the following processes.

Process 1

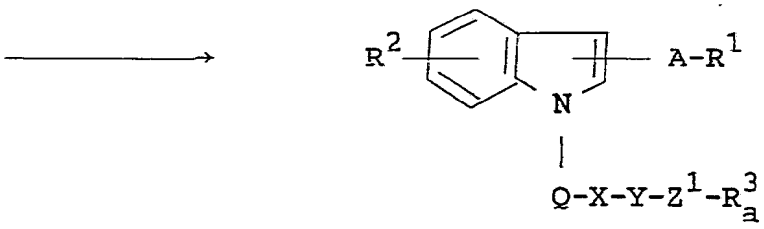


(II)
or a salt thereof

+

$W^1 - R_a^3$

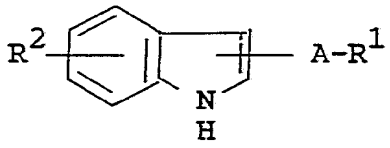
(III)
or a salt thereof



(I-a)

or a salt thereof

Process 2



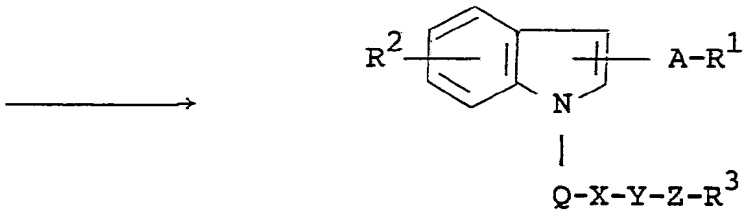
(IV)

or a salt thereof

+ W^2-Q-X-Y-Z-R^3

(V)

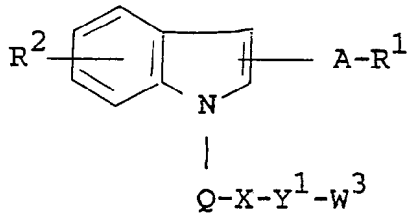
or a salt thereof



(I)

or a salt thereof

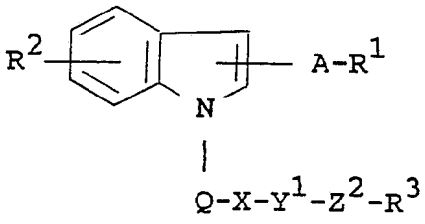
Process 3



(VI)
or a salt thereof

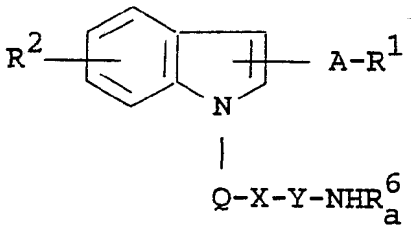
+ $H-Z^2-R^3$

(VII)
or a salt thereof



(I-b)
or a salt thereof

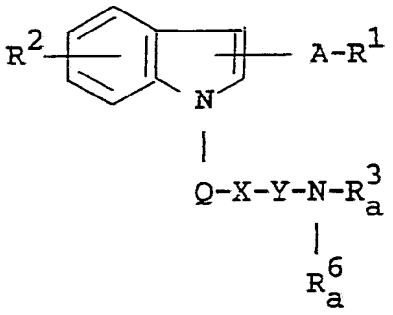
Process 4



(VIII)
or a salt thereof

+ $W^1 - R_a^3$

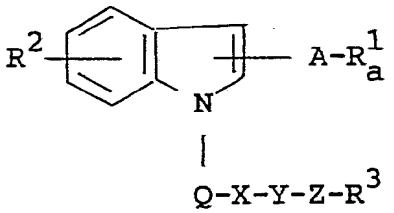
(III)
or a salt thereof



(I-c)

or a salt thereof

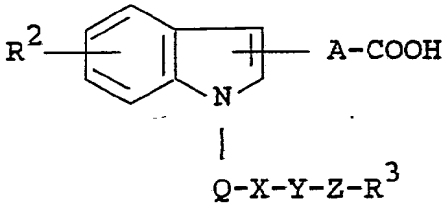
Process 5



Elimination of the carboxy protective group ⟶

(I-d)

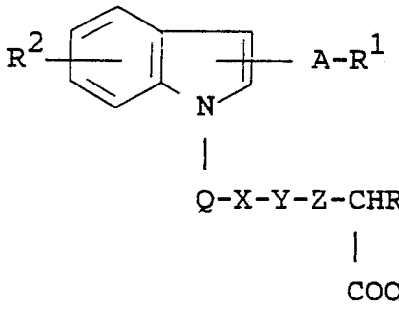
or a salt thereof



(I-e)

or a salt thereof

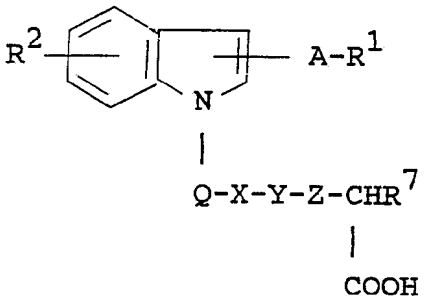
Process 6



Elimination of the carboxy protective group

(I-f)

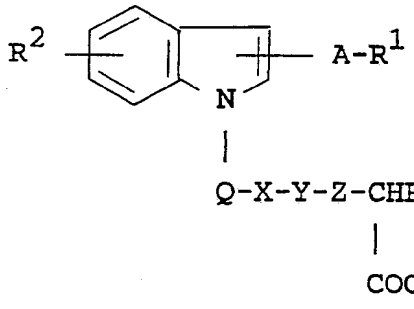
or a salt thereof



(I-g)

or a salt thereof

Process 7



+ H - R^9

(VII)

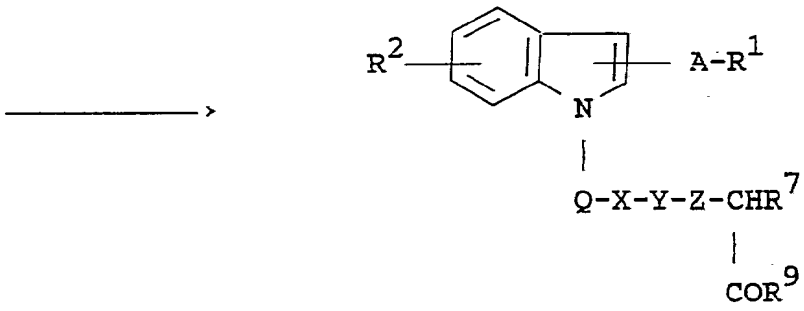
or its reactive derivative at the amino group

or a salt thereof

(I-g)

or its reactive derivative at the carboxy group

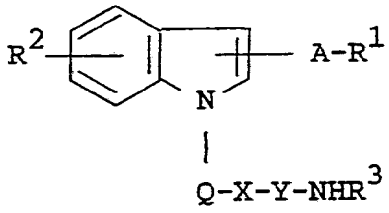
or a salt thereof



(I-h)

or a salt thereof

Process 8



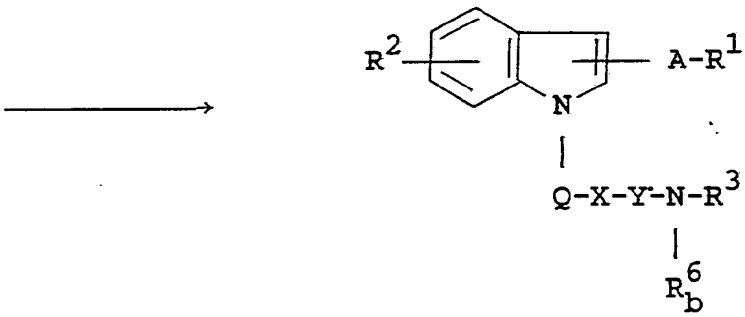
(X)

or a salt thereof

+ $W^4 - R_b^6$

(XI)

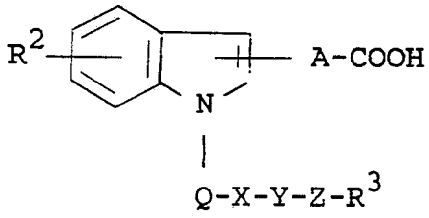
or a salt thereof



(I-i)

or a salt thereof

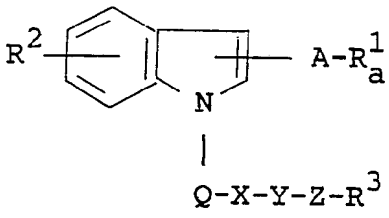
Process 9



Introduction of the carboxy protective group

(I-e)

or a salt thereof



(I-d)

or a salt thereof

wherein R^1, R^2, R^3, R^4, R^5, A, Q, X, Y and Z are each as defined above,

R^1_a is protected carboxy,

R^3_a is ar(lower)alkyl which may have suitable substituent(s) or a group of the formula :

$$-(CO)_n - N\bigcirc$$

in which $-N\bigcirc$ and n are each as defined above,

R^6_b is lower alkyl,

ar(lower)alkyl which may have suitable substituent(s) or amino protective group,

R^7 is aryl which may have suitable substituent(s),

R^8 is carboxy protective group,

R^9 is amino which may have suitable substituent(s),

W^1, W^2, W^3 and W^4 are each acid residue,

Y^1 is lower alkylene,

Z^1 is $-O-$, $-S-$ or $-\overset{\overset{R^6_a}{|}}{N}-$ in which R^6_a is lower alkyl or amino protective group, and

Z^2 is $-O-$, $-S-$ or $-\overset{\overset{R^6}{|}}{N}-$ in which R^6 is as defined above.

Suitable salts of the compounds (I) are conventional non-toxic, pharmaceutically acceptable salt and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like, and the preferable example thereof is an acid addition salt.

With respect to the salt of the compounds (I-a) to

(I-i), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X) and (XI) in Processes 1 to 9, the suitable examples of the salts of these compounds are to be referred to those as exemplified for the object compound (I).

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched one, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, and the like, preferably one having 1 to 4 carbon atoms.

The term "halogen" means fluoro, chloro, bromo and iodo.

Suitable "lower alkylene" means straight or branched bivalent lower alkane such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, propylene, and the like, which may be substituted by oxo.

Suitable "acid residue" may include halogen (e.g. fluoro, chloro, bromo, iodo), acyloxy (e.g. acetoxy, tosyloxy, mesyloxy, etc.), aryloxy (e.g. phenoxy, etc.) and the like.

Suitable "lower alkenylene" may include one having 2 to 6 carbon atoms such as vinylene, propenylene, and the like.

Suitable "aryl which may have suitable substituent(s)" may include a conventional group such as aryl (e.g. phenyl, naphthyl, etc.), substituted aryl, for example, lower alkylaryl (e.g. tolyl, xylyl, mesityl,

cumenyl, isobutylphenyl, isopentylphenyl, etc.), haloaryl (e.g. chlorophenyl, bromophenyl, dichlorophenyl, etc.), lower alkoxyaryl (e.g. isopropoxyphenyl, etc.), lower alkylcarbamoylaryl (e.g. t-butylcarbamoylphenyl, etc.), and the like.

Suitable "ar(lower)alkyl which may have suitable substituent(s)" may include a conventional group such as ar(lower)alkyl (e.g. trityl, benzhydryl, benzyl, phenethyl, naphthylmethyl, etc.), substituted ar(lower)alkyl, for example, ar(lower)alkyl substituted by one or more substituents such as lower alkyl as mentioned above, halogen as mentioned above, cyano, carboxy, protected carboxy as mentioned below, aryl which may have suitable substituent(s) as mentioned above, amidated carboxy as mentioned below and oxo. Specific examples of thus defined "ar(lower)alkyl which may have suitable substituents" may be methylbenzyl, propylbenzyl, isobutylbenzyl, methylphenylethyl, isobutylphenylethyl, methylphenylpropyl, isobutylphenylpropyl, methylphenylpentyl, isobutylphenylpentyl, bis(methylphenyl)methyl, bis(propylphenyl)methyl, bis(butylphenyl)methyl, bis(isobutylphenyl)methyl, bis(chlorophenyl)methyl, (cyano)(isobutylphenyl)methyl, (carboxy)(isobutylphenyl)methyl, (benzyloxycarbonyl)(isobutylphenyl)methyl, (N,N-diethylcarbamoyl)(isobutylphenyl)methyl, (t-butylcarbamoyl)(isobutylphenyl)methyl, (phenylcarbamoyl)(isobutylphenyl)methyl, (isobutylphenylcarbamoyl)(isobutylphenyl)methyl, etc.], benzoyl, isobutylbenzoyl, and the like.

Suitable "amino protective group" may be a conventional protective group, which is used in the field of organic chemistry, that is, may include acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl,

etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), and the like.

Suitable "protected carboxy" may include an esterified carboxy group.

Suitable examples of the ester moiety of an "esterified carboxy" may be the ones such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester (e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-acetoxypropyl ester, 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)-pentanoyloxyethyl ester, etc.) lower alkanesulfonyl(lower)alkyl ester (e.g. 2-mesylethyl ester, etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkoxycarbonyloxy(lower)alkyl ester (e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.), phtahlidylidene(lower)alkyl ester, or (5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester (e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester,

(5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.; lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.); lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.); ar(lower)alkyl ester which may have at least one suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.); aryl ester which may have at least one suitable substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.); phthalidyl ester; and the like.

Preferable examples of the esterified carboxy as mentioned above may include lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, 1-cyclopropylethoxycarbonyl, etc.).

Suitable "carboxy protective group" may be the ester moiety of the above defined "protected carboxy" and may include lower alkyl (e.g. methyl, ethyl, etc.), ar(lower)alkyl (e.g. benzyl, etc.), and the like.

Suitable "amino which may have suitable substituent(s)" is conventional one used in a pharmaceutical field and may include amino, mono or di(lower)alkylamino (e.g. methylamino, dimethylamino, ethylamino, diethylamino, butylamino, t-butylamino, etc.), arylamino (e.g. phenylamino, etc.), lower alkylarylamino (e.g. isobutylphenylamino, etc.), and the like.

Suitable "heterocyclic group containing nitrogen atom" may include saturated or unsaturated monocyclic or

polycyclic heterocyclic group containing at least one nitrogen atom. Especially preferable heterocyclic group may be 5- or 6- membered aliphatic heteromonocyclic group (e.g. morpholinyl, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.), unsaturated condensed heterocyclic group such as dibenzo[6 or 7-membered unsaturated]heteromonocyclic group (e.g. phenoxazinyl, phenothiazinyl, 10,11-dihydro-5H-dibenzoazepinyl, etc.), and the like.

Suitable "amidated carboxy" may carbamoyl which may have suitable substituent(s) and may include carbamoyl, mono or di(lower)alkylcarbamoyl (e.g. methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl diethylcarbamoyl, butylcarbamoyl, t-butylcarbamoyl, etc.), lower alkylaryl-carbamoyl (e.g. isobutylphenylcarbamoyl, etc.), and the like.

Suitable "6H-dibenzo[b,d]pyranyl which may have suitable substituent(s)" may include 6H-dibenzo[b,d]pyranyl substituted by lower alkyl as mentioned above (e.g. 8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyranyl, etc.), and the like.

Particularly, the preferred embodiments of R^1, R^2, R^3, A, Q, X, Y and Z are as follows.

R^1 is carboxy;

lower alkoxycarbonyl, more preferably C_1-C_4 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, etc.); or

ar(lower)alkoxycarbonyl, more preferably mono- or di- or triphenyl(C_1-C_4)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.),

R^2 is hydrogen;

lower alkyl, more preferably C_1-C_4 alkyl (e.g. methyl, etc.); or

halogen (e.g. chloro, etc.),

R^3 is aryl which may be substituted by one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and lower alkylcarbamoyl more preferably phenyl which may be substituted by one to three substituent(s) selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and C_1-C_4 alkylcarbamoyl (e.g. phenyl, isobutylphenyl, isopentylphenyl, isopropoxyphenyl, bromophenyl, dichlorophenyl, t-butylcarbamoylphenyl, etc.);
ar(lower)alkyl which may be substituted by one to three substituents selected from the group consisting of lower alkyl, halogen, cyano, carboxy, protected carboxy, amidated carboxy, and oxo, more preferably mono- or di- or triphenyl(lower)alkyl which may be substituted by one or two the groups selected from lower alkyl, halogen, cyano, carboxy, phenyl(lower)-alkoxycarbonyl, mono or di(lower)alkylcarbamoyl, phenylcarbamoyl and lower alkylphenylcarbamoyl, most preferably mono- or di- or triphenyl(C_1-C_6)alkyl which may be substituted by the group selected from (C_1-C_4)alkyl, halogen, cyano, carboxy, phenyl(C_1-C_4)alkoxycarbonyl, mono or di(C_1-C_4)alkylcarbamoyl, phenylcarbamoyl, (C_1-C_4)alkylphenylcarbamoyl and oxo (e.g. benzyl, propylbenzyl, isobutylbenzyl, isobutylphenylethyl, isobutylphenylpropyl, isobutylphenylpentyl, bis(isobutylphenyl)methyl, dichlorobenzyl, bis(chlorophenyl)methyl, (cyano)(isobutylphenyl)methyl, (carboxy)(isobutylphenyl)methyl, (benzyloxycarbonyl)-(isobutylphenyl)methyl, (N,N-diethylcarbamoyl)-(isobutylphenyl)methyl, (t-butylcarbamoyl)-(isobutylphenyl)methyl, (phenylcarbamoyl)-(isobutylphenyl)methyl, (isobutylphenylcarbamoyl)-

(isobutylphenyl)methyl, benzoyl, isobutylbenzoyl, etc.);

5- or 6- membered aliphatic heteromonocycliccarbonyl (e.g. piperidylcarbonyl, etc.); or

unsaturated condensed heterocyclic group (e.g. phenoxazinyl, phenothiazinyl, 10,11-dihydro-5H-dibenzo[b,f]azepinyl, etc.),

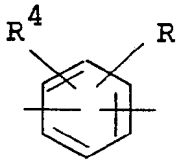
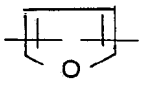
A is lower alkylene which may be substituted by oxo, more preferably C_1-C_4 alkylene which may be substituted by oxo (e.g. ethylene, trimethylene, oxotrimethylene, etc.); or

lower alkenylene, more preferably C_2-C_4 alkenylene (e.g. propenylene, etc.),

Q is carbonyl;

sulfonyl; or

lower alkylene, more preferably C_1-C_4 alkylene (e.g. methylene, etc.),

X is  or 

in which R^4 is hydrogen; or lower alkyl, more preferably C_1-C_4 alkyl (e.g. methyl, etc.),

R^5 is hydrogen; lower alkyl, more preferably C_1-C_4 alkyl (e.g. methyl, etc.); or

ar(lower)alkylamino which may be substituted by the group(s) selected from lower alkyl or lower alkoxycarbonyl, more preferably C_1-C_4 alkylbenzylamino or N-C_1-C_4 alkoxycarbonyl-N-C_1-C_4 alkylbenzylamino (e.g. isobutylbenzylamino,

N-t-butoxycarbonyl-N-isobutylbenzylamino, etc.),

Y is bond; or
lower alkylene, more preferably C_1-C_4 alkylene (e.g. methylene, etc.), and

Z is bond;
lower alkylene, more preferably C_1-C_4 alkylene (e.g. methylene, etc.);
lower alkenylene, more preferably C_2-C_6 alkenylene (e.g. propenylene, etc.),
O ;
S; or
N-R^6
in which R^6 is lower alkyl, preferably C_1-C_4 alkyl (e.g. methyl, ethyl, etc.);
lower alkoxycarbonyl, preferably C_1-C_4 alkoxycarbonyl (e.g. t-butoxycarbonyl, etc.);
ar(lower)alkyl which may be substituted by lower alkyl, more preferably mono- or di- or triphenyl(lower)alkyl which may be substituted by lower alkyl, most preferably mono- or di- or triphenyl(C_1-C_6)alkyl which may be substituted by C_1-C_4 alkyl (e.g. benzyl, isobutylbenzyl, etc.); or
X-Y-Z-R^3 is 6H-dibenzo[b,d]pyranyl which may be substituted by lower alkyl, more preferably 6H-dibenzo[b,d]pyranyl substituted by C_1-C_4 alkyl (e.g. 8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyranyl, etc.).

The processes 1 to 9 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I-a) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

This reaction is usually carried out in a solvent such as alcohol [e.g. methanol, ethanol, etc.], dichloromethane, benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), tri(lower)alkylamine [e.g. trimethylamine, triethylamine, diisopropylethylamine, etc.], pyridine or its derivative [e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.], or the like. In case that the base to be used is liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction can be carried out under cooling, at room temperature or under warming or heating.

Process 2

The object compound (I) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 3

The object compound (I-b) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

Process 4

The object compound (I-c) or a salt thereof can be prepared by reacting the compound (VII) or a salt thereof with the compound (III) or a salt thereof.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

The present reaction includes, within its scope, the case that when R^1 is carboxy, it is protected during the reacting or at the post-treating step of the present process.

Process 5

The object compound (I-e) or a salt thereof can be prepared by subjecting the compound (I-d) or a salt thereof to elimination reaction of the carboxy protective group.

In the present elimination reaction, all conventional methods used in the elimination reaction of the carboxy protective group, for example, hydrolysis, reduction, elimination using Lewis acid, etc. are applicable. When the carboxy protective group is an ester, it can be eliminated by hydrolysis or elimination using Lewis acid.

The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-one, 1,4-diazabicyclo[2.2.2]octane, 1,5-diazabicyclo[5.4.0]undecene-5 or the like.
The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

The reaction temperature is not critical, and it may suitable be selected in accordance with the kind of the carboxy protective group and the elimination method.

The elimination using Lewis acid is preferable to eliminate substituted or unsubstituted ar(lower)alkyl ester and carried out by reacting the compound (Ig) or a salt thereof with Lewis acid such as boron trihalide (e.g. boron trichloride, boron trifluoride, etc.), titanium tetrahalide (e.g. titanium tetrachloride, titanium tetrabromide, etc.), tin tetrahalide (e.g. tin tetrachloride, tin tetrabromide, etc.), aluminum halide (e.g. aluminum chloride, aluminum bromide, etc.), trihaloacetic acid (e.g. trichloroacetic acid, trifluoroacetic acid, etc.) or the like. This elimination reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane, etc.), alkylene halide (e.g. methylene chloride, ethylene chloride, etc.), diethyl ether, carbon disulfide or any other solvent which does not adversely affect the reaction. These solvents may be used as a mixture thereof.

The reduction elimination can be applied preferably for elimination of the protective group such as halo(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl, etc.) ester, ar(lower)alkyl (e.g. benzyl, etc.) ester or the like.

The reduction method applicable for the elimination reaction may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chromium compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or an inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and conventional catalytic reduction in the pressure of a conventional metallic catalyst (e.g. palladium carbon, Raney nickel, etc.).

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient

temperature or under warming.

Process 6

The object compound (I-g) or a salt thereof can be prepared by subjecting the compound (I-f) or a salt thereof to elimination reaction of the carboxy protective group.

This reaction can be carried out in substantially the same manner as Process 5, and therefore the reaction mode and reaction conditions [e.g. bases, acids, reducing agents, catalysts, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 5.

Process 7

The object compound (I-h) or a salt thereof can be prepared by reacting a compound (I-g) or its reactive derivative at the carboxy group or a salt thereof with a compound (IX) or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivative at the amino group of the compound (IX) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (IX) wit a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (IX) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (IX) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative at the carboxy group of the compound (I-g) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may

be an acid chloride; an acid azide; a mixed acid anhydride within acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (I-g) to be used.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used

in a mixture with water.

In this reaction, when the compound (I-g) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 8

The object compound (I-i) or a salt thereof can be

prepared by reacting the compound (X) or a salt thereof with the compound (XI) or a salt thereof.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

The present reaction includes, within its scope, the case that when R^1 is carboxy, it is protected during the reaction or at the post-treating step of the present process.

Process 9

The object compound (I-d) or a salt thereof can be prepared by subjecting the compound (I-e) or a salt thereof to introduction reaction of the carboxy protective group.

The reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvent,s reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

The starting compounds (II), (IV) and (VI) can be prepared by the details of which are shown in Preparations mentioned below, or a conventional manner.

The object compound (I) of the present invention can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The object compound (I) thus obtained can be converted to its salt by a conventional method.

The object compound (I) of the present invention is

useful as a testosteron 5α-reductase inhibitor and effective to testosteron 5α-reductase mediated diseases such as prostatism, prostatic hypertrophy, prostatic cancer, alopecia, hirsutism (e.g. female hirsutism, etc.), androgenic alopecia (or male-pattern baldness), acne (e.g. acne vulgarism, pimple etc.), other hyperandrogenism, and the like.

In order to illustrate the usefulness of the object compounds (I), pharmacological activity of representative compounds of the present invention is shown below.

[1] Test Compound :

(1) 4-[1-[3-(3-Isobutylphenoxymethyl)benzoyl]indol-3-yl]-butyric acid

(2) 4-[1-[4-(4-Isobutylbenzyloxy)benzyl]indol-3-yl]-butyric acid

(3) 4-[1-[4,5-Dimethyl-3-[1-(4-isobutylphenyl)ethoxy]-benzoyl]indol-3-yl]butyric acid

(4) 4-[1-[3-(3-Bromophenoxymethyl)benzoyl]indol-3-yl]-butyric acid

(5) 4-[1-[3-[N-(4-Isobutylbenzoyl)(3-isobutylphenyl)-aminomethyl]benzoyl]indol-3-yl]butyric acid

(6) 4-[1-[2,3-Dimethyl-5-(3-isobutylphenoxymethyl)-benzoyl]indol-3-yl]butyric acid

(7) 4-[1-[3-[2-(4-Isobutylphenyl)vinyl]benzoyl]indol-3-yl]butyric acid

(8) 4-[1-[4-[Bis(4-isobutylphenyl)methoxy]benzoyl]-indol-3-yl]butyric acid

(9) 4-[1-[4-[2-(4-Isobutylphenyl)propyl]benzoyl]-indol-3-yl]butyric acid

[2] Inhibitory activity on testosterone 5α-reductase in rats :

Test Methods

i) Materials

1,2,6,7-^{3}H-Testosterone (85-105 Ci/mmol) :
1,2,6,7-^{3}H-Testosterone (85-105 Ci/mmol) is a mixture of 1,2,6,7-^{3}H-testosterone and testosterone which includes 85-105 Ci of 1,2,6,7-^{3}H-testosterone per mmol of testosterone and is purchased from New England Nuclear, Boston, Mass., U.S.A..

Aquazol-2 (Aquazol-2- Universal LSC Cocktail) :
trademark, purchased from New England Nuclear, Boston, Mass., U.S.A.

ii) Preparation of prostatic testosterone 5α-reductase

Mature Sprague-Dawley male rats (7-8 weeks old) were sacrificed by diethyl ether. The ventral prostates were dissected to be free of their capsules and their combined volume was measured by displacement in several milliliters of ice-cold medium A (0.32 M sucrose, 0.1 mM dithiothreitol and 20 mM sodium phosphate, pH 6.5). Unless specified, all the following procedures were carried out at 0-4°C. The prostates were drained, minced, and then homogenized in 3-4 tissue volumes of medium A with Pyrex-glass homogenizer. The homogenate was

fractions by differential centrifugations at 3,000 g for 15 minutes. The resulting pellets were resuspended in medium A. The suspension (20-30 mg protein/ml) was stored at -80°C.

iii) Testosterone 5α-reductase assay

The reaction solution contains 1 mM dithiothreitol, 40 mM sodium phosphate pH 6.5, 50 μM NADPH, 1,2,6,7-^{3}H-testosterone/testosterone (2.2×10^{-9} M) and the suspension prepared above (0.8 mg of protein) in a total volume of 565 μl. Test Compound was added in 10 μl of 10% ethanol whereas control tubes received the same volume of 10% ethanol. The reaction was started with the addition of the enzyme suspension. After incubation at 37°C for 30 minutes, the reaction was extracted with 1 ml of ethyl acetate. Fifty μl of ethyl acetate phase was chromatographed on a Merck silica plastic sheet Kieselgel 60 F_{254}, using ethyl acetate : cyclohexane (1:1) as the developing solvent system. The plastic sheet was air dried and cut the testosterone and the 5α-dihydrotestosterone areas. The radioactivity was counted in 5 ml of Aquazol-2 in Packard scintillation counter (PACKARD TRI - CARB 4530), and an inhibitory ratio was calculated.

[3] Test Results :

Compound	IC_{50} (M)
(1)	1.7×10^{-9}
(2)	1.1×10^{-9}
(3)	1.6×10^{-9}
(4)	6.3×10^{-9}
(5)	5.7×10^{-9}

(6)	2.7×10^{-9}
(7)	1.4×10^{-9}
(8)	7.5×10^{-9}
(9)	2.5×10^{-10}

For therapeutic or preventive administration, the object compound (I) of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparation may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, lemonade, lotion and the like.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases or conditions, a kind of the compound (I) to be applied, etc. In general amounts between 0.01 mg and about 500 mg or even more per day may be administered to a patient. An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of the object compound (I) of the present invention may be used in treating diseases.

The following Preparations and Example are given for the purpose of illustrating the present invention.

Preparation 1

To a solution of 2,3-xylenol (19.45 g) in dichloromethane (300 ml) was added a solution of bromine (8.20 ml) in dichloromethane (20 ml) at -20°C. After stirred for 1.5 hours, the mixture was washed with water. The solution was dried over magnesium sulfate and the solvent was removed in vacuo. The residue was crystallized with n-hexane to give a white solid of 4-bromo-2,3-dimethylphenol (16.8 g).

mp : 87-88°C

IR ($CDCl_3$, δ) : 2.23 (3H, s), 2.37 (3H, s), 4.75 (1H, br s), 6.52 (1H, d, J=9Hz), 7.24 (1H, d, J=9Hz)

Preparation 2

To a solution of 3,4-dimethylbenzoic acid (10.0 g) in acetic acid (300 ml) were added nitric acid (47 ml), water (33 ml) and bromine (11.7 g) at 25°C. A solution of silver nitrate (14.7 g) in water (70 ml) was added dropwise to the mixture at 25°C over 1 hour. The reaction mixture was poured into a mixture of ethyl acetate (1 ℓ) and water (1.5 ℓ). The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation at the solvent, the residue was purified by recrystallization from ethanol to give 3-bromo-4,5-dimethylbenzoic acid (6.16 g) as yellow crystals.

NMR ($CDCl_3$, δ) : 2.40 (3H, s), 2.46 (3H, s), 7.82 (1H, d, J=1Hz), 8.28 (1H, d, J=1Hz)

Preparation 3

Triphenylphosphine (7.23 g) was added to a mixture of 3-bromo-4,5-dimethylbenzyl alcohol (3.95 g) and carbon tetrabromide (9.14 g) in ether (100 ml) at 0°C, and the mixture was allowed to warm up to 25°C. The reaction

mixture was stirred at 25°C for 2 hours, and then the precipitates were filtered off. The filtrate was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel (100 g) eluting with chloroform to give 3-bromo-4,5-dimethylbenzyl bromide (4.15 g) as colorless crystals.

NMR ($CDCl_3$, δ) : 2.32 (3H, s), 2.46 (3H, s), 4.38 (2H, s), 7.12 (1H, d, J=1Hz), 7.45 (1H, d, J=7Hz)

Preparation 4

The following compound was obtained according to a similar manner to that of Preparation 3.

1-(4-Isobutylphenyl)ethyl bromide

bp : 77-80°C/0.2 mmHg

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.86 (1H, m), 2.05 (3H, d, J=7.5Hz), 2.46 (2H, d, J=7.5Hz), 5.23 (1H, q, J=7.5Hz), 7.11 (2H, d, J=8Hz), 7.34 (2H, d, J=8Hz)

Preparation 5

To a solution of 4-isobutylacetophenone (100 g) in isopropyl alcohol (500 ml) was added sodium borohydride (25.76 g). The mixture was stirred for 16 hours at room temperature. To the mixture was added water (500 ml) and diluted hydrochloric acid (600 ml). The organic layer was extracted with ethyl acetate (300 ml) and washed with water. The solution was dried over magnesium sulfate. The solvent was removed in vacuo to give colorless oil of 1-(4-isobutylphenyl)ethanol (101.1 g).

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.49 (3H, d, J=6Hz), 1.86 (1H, m), 2.47 (2H, d, J=7.5Hz), 4.88 (1H, q, J=6Hz), 7.13 (2H, d, J=8Hz), 7.28 (2H, d, J=8Hz)

Preparation 6

To a solution of isobutyltriphenylphosphonium bromide (48.8 g) in tetrahydrofuran (600 ml) was added a solution of potassium t-butoxide (13.57 g) in tetrahydrofuran (230 ml). The mixture was stirred at room temperature for 1 hour. To the mixture was added a solution of 1,4-cyclohexanedione mono-ethylene acetal (10.0 g) in tetrahydrofuran (100 ml). The mixture was stirred at room temperature for 3 days and partitioned between diethyl ether and water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by chromatography on silica gel (300 g) using a mixture of n-hexane and 5% ethyl acetate as the eluent. Appropriate fractions were combined and evaporated to give 4-(2-methyl-1-propylidene)cyclohexanone ethylene acetal (12.16 g) as a colorless oil.

NMR ($CDCl_3$, δ) : 0.94 (6H, d, J=7Hz), 1.6-1.8 (4H, m), 2.1-2.3 (4H, m), 2.4-2.6 (1H, m), 3.97 (4H, s), 4.98 (1H, d, J=9Hz)

Preparation 7

6N-Hydrochloric acid (35 ml) was added to a solution of 4-(2-methyl-1-propylidene)cyclohexanone ethylene acetal (12.16 g) in 1,4-dioxane (70 ml) and methanol (35 ml). The mixture was stirred at room temperature for 20 hours and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo to give 4-(2-methyl-1-propylidene)cyclohexane (9.43 g) as a colorless oil.

NMR ($CDCl_3$, δ) : 0.98 (6H, d, J=7Hz), 2.3-2.7 (9H, m), 5.18 (1H, d, J=9Hz)

Preparation 8

To a solution of 4-(2-methyl-1-propylidene)-

cyclohexanone (1.0 g) in acetic acid (20 ml) was added 10% palladium on carbon (0.2 g). The mixture was hydrogenated for 19 hours at room temperature. The catalyst was filtered off and the filtrate was partitioned between ethyl acetate and water. The organic layer was washed with saturated sodium bicarbonate aqueous solution and water and dried over magnesium sulfate. The solvent was removed in vacuo to give 4-isobutylcyclohexane (1.01 g) as a colorless oil.

NMR ($CDCl_3$, δ) : 0.90 (3H, d, J=7Hz), 1.16 (2H, t, J=7.5Hz), 1.2-1.5 (2H, m), 1.6-1.9 (2H, m), 1.9-2.1 (2H, m), 2.3-2.4 (4H, m)

Preparation 9

To a solution of diethyl carbonate (6.19 g) and potassium tert-butoxide (4.31 g) in tetrahydrofuran (50 ml) was added a solution of 4-isobutylcyclohexanone (2.48 g) in tetrahydrofuran (35 ml). The mixture was allowed to reflux for 1 hour and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was distilled at reduced pressure to give 2-ethoxycarbonyl-4-isobutylcyclohexanone (2.99 g) as a colourless oil.

bp : 92°C/0.4 mmHg

NMR($CDCl_3$, δ) : 0.8-1.0 (1H, m), 0.89 (6H, d, J=6Hz), 1.1-1.4 (3H, m), 1.31 (3H, t, J=7Hz), 1.4-1.9 (5H, m), 2.2-2.3 (2H, m), 4.22 (2H, q, J=7Hz)

Preparation 10

1M solution of borane in tetrahydrofuran (40.5 ml) was added to a solution of 3-bromo-4,5-dimethylbenzoic acid (4.22 g) in tetrahydrofuran (20 ml) at 0°C, and then the mixture was allowed to warm up to 25°C. The reaction mixture was stirred at 25°C for 2 hours and poured into a

mixture of ether and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave 3-bromo-4,5-dimethylbenzyl alcohol (4.00g) as an oil.

NMR ($CDCl_3$, δ) : 2.33 (3H, s), 2.36 (3H, s), 4.60 (2H, s), 7.09 (1H, d, J=1Hz), 7.42 (1H, d, J=1Hz)

Preparation 11

A mixture of 1-bromo-1-(4-isobutylphenyl)ethane (8.70 g) and triphenylphosphine (9.47 g) in xylene (100 ml) was refluxed for 10 hours. After evaporation of the solvent, the residue was washed with hexane to give 1-(4-isobutylphenyl)ethyltriphenylphosphonium bromide (12.69 g) as powder.

NMR ($CDCl_3$, δ) : 6.65 (1H, q, J=6Hz)

Preparation 12

4-Isobutylbenzoyl chloride (1.32 g) was added to a solution of 4-isobutylaniline (1.0 g) and triethylamine (0.68 g) in dichloromethane (20 ml). The mixture was stirred at 0°C for 1 hour and poured into ice water. The organic layer was washed with water, dried over magnesium sulfate, and evaporated. The residue was washed with n-hexane to give N-(4-isobutylbenzoyl)-4-isobutylaniline (1.82 g) as a white powder.

mp : 162°C

NMR ($CDCl_3$, δ) : 0.91 (6H, d, J=7Hz), 0.92 (6H, d, J=7Hz), 1.8-2.0 (2H, m), 2.46 (2H, d, J=7Hz), 2.54 (2H, d, J=7Hz), 7.14 (2H, d, J=8Hz), 7.25 (2H, d, J=8Hz), 7.54 (2H, d, J=8Hz), 7.78 (2H, d, J=8Hz)

Preparation 13

The following compounds were obtained according to a

similar manner to that of Preparation 12.

(1) N-Benzoyl-4-isobutylaniline
mp : 128°C
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7Hz), 1.85 (1H, m), 2.46 (2H, d, J=7Hz), 7.15 (2H, d, J=8Hz), 7.4-7.6 (5H, m), 7.7-7.9 (3H, m)

(2) Methyl 3-[N-(4-isobutylphenyl)carbamoyl]benzoate
mp : 116°C
NMR ($CDCl_3$, δ) : 0.91 (6H, d, J=7Hz), 1.86 (1H, m), 2.47 (2H, d, J=7Hz), 3.95 (3H, s), 7.15 (2H, d, J=8Hz), 7.56 (1H, t, J=7.5Hz), 7.56 (2H, d, J=8Hz), 7.98 (1H, br s), 8.13 (1H, dt, J=2Hz, 7.5Hz), 8.20 (1H, dt, J=2Hz, 7.5Hz), 8.47 (1H, t, J=7.5Hz)

(3) N-(4-Isobutylbenzoyl)-3-isobutylaniline
mp : 69-70°C
NMR ($CDCl_3$, δ) : 0.92 (12H, d, J=7Hz), 1.8-2.0 (2H, m), 2.48 (2H, d, J=7Hz), 2.54 (2H, d, J=7Hz), 6.94 (1H, d, J=7.5Hz), 7.2-7.4 (4H, m), 7.4-7.5 (2H, m), 7.3-7.4 (3H, m)

Preparation 14

To a solution of 1-(4-isobutylphenyl)-ethyltriphenylphosphonium bromide (7.48 g) in tetrahydrofuran (30 ml) was added a solution of potassium tert-butoxide (1.67 g) in tetrahydrofuran (20 ml). The mixture was stirred at room temperature for 1 hour. To the mixture was added a solution of 3-bromobenzaldehyde (1.6 ml) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 3 hours, and portioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate and

evaporated. The residue was purified by chromatography on silica gel (200 g) using a mixture of n-hexane and 2% ethyl acetate as a eluent. Appropriate fractions were combined and evaporated to give 3-[2-(4-isobutylphenyl)-1-propenyl]phenyl bromide as a colourless oil (2.03 g).

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7Hz), 1.88 (1H, m), 2.26 (3H, d, J=1Hz), 2.50 (2H, d, J=7Hz), 6.75 (1H, d, J=1Hz), 7.1-7.5 (3H, m), 7.15 (2H, d, J=8Hz), 7.43 (2H, d, J=8Hz), 7.50 (1H, s)

Preparation 15

The following compounds were obtained according to a similar manner to that of Preparation 14.

(1) 3-Cyano-4'-isobutylstilbene

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.85 (1H, m), 2.50 (2H, d, J=6Hz), 7.00 (1H, d, J=17Hz), 7.14 (1H, d, J=17Hz), 7.16 (2H, d, J=8Hz), 7.40-7.55 (4H, m), 7.70 (1H, m), 7.75 (1H, m)

(2) Methyl 4-[2-(4-isobutylphenyl)-1-propenyl]benzoate

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=5Hz), 1.90 (1H, m), 2.30 (3H, d, J=0.4Hz), 3.90 (3H, s), 6.82 (1H, s), 7.15 (2H, d, J=7.5Hz), 7.40 (2H, d, J=7.5Hz), 7.45 (2H, d, J=10Hz), 8.05 (2H, d, J=10Hz)

(3) 4-(2-Methyl-1-propenyl)phenyl phenyl ether

NMR ($CDCl_3$, δ) : 1.89 (6H, dd, J=2Hz, 7Hz), 6.23 (1H, br s), 6.9-7.4 (9H, m)

Preparation 16

A mixture of 4-bromobenzylmethyl ether (2.61 g) and magnesium (474 g) in tetrahydrofuran (40 ml) was refluxed for 1 hour. The mixture was allowed to cool to 25°C, and

then a solution of 4-isobutylcyclohexanone (2.0 g) in tetrahydrofuran (30 ml) was added at 25°C. After stirred at 25°C for 1 hour, the reaction mixture was quenched with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel (50 g) eluting with a mixture of ethyl acetate and hexane (1:10 to 1:6) to give 4-(1-hydroxy-4-isobutylcyclohexyl)benzyl methyl ether (2.51 g) as an oil.

NMR (CD_3OD, δ) : 0.68 (6H, d, J=7.5Hz), 0.80-1.05 (3H, m), 1.35-1.75 (7H, m), 2.05-2.24 (2H, m), 3.20 (3H, s), 4.38 (2H, s), 7.13 (2H, d, J=8Hz), 7.32 (2H, d, J=8Hz)

Preparation 17

To a suspension of sodium hydride (60% dispersion in mineral oil) (0.35 g) in dimethylformamide (15 ml) was added a solution of N-(4-isobutylbenzoyl)-4-isobutylaniline (1.81 g) in dimethylformamide (10 ml). The mixture was stirred at room temperature for 30 minutes and cooled at 0°C. To the mixture was added a solution of methyl 3-bromomethylbenzoate (1.34 g) in dimethylformamide (5 ml). The mixture was stirred at 0°C for 1 hour and partitioned between ethyl acetate and 7% hydrochloric acid. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (60 g) using a mixture of n-hexane and ethyl acetate (3:1) as the eluent. Appropriate fractions were combined and evaporated to give methyl 3-[N-(4-isobutylbenzoyl)-N-(4-isobutylphenyl)aminomethyl]benzoate (2.13 g) as a colourless foam.

NMR ($CDCl_3$, δ) : 0.79 (12H, d, J=7Hz), 1.6-1.9 (2H, m), 2.35 (2H, d, J=7Hz), 2.37 (2H, d, J=7Hz),

3.89 (3H, s), 5.16 (2H, s), 6.78 (2H, d, J=8Hz), 6.92 (2H, d, J=8Hz), 7.23 (2H, d, J=8Hz), 7.38 (1H, t, J=7.5Hz), 7.58 (1H, d, J=7.5Hz), 7.93 (1H, d, J=7.5Hz), 7.95 (1H, s)

Preparation 18

The following compounds were obtained according to a similar manner to that of Preparation 17.

(1) Methyl 3-[N-(4-isobutylbenzoyl)-N-(3-isobutylphenyl)-aminomethyl]benzoate
NMR ($CDCl_3$, δ) : 0.66 (6H, d, J=7Hz), 0.82 (6H, d, J=7Hz), 1.52 (1H, m), 1.75 (1H, m), 2.24 (2H, d, J=7Hz), 2.35 (2H, d, J=7Hz), 3.90 (3H, s), 5.17 (2H, s), 6.57 (1H, s), 6.8-7.0 (2H, m), 6.92 (1H, d, J=7.5Hz), 7.08 (1H, t, J=7.5Hz), 7.25 (2H, d, J=8Hz), 7.37 (1H, t, J=7.5Hz), 7.58 (1H, d, J=7.5Hz), 7.93 (1H, d, J=7.5Hz), 7.94 (1H, br s)

(2) Methyl 3-[N-t-butoxycarbonyl-N-(4-isobutylphenyl)-aminomethyl]benzoate
NMR ($CDCl_3$, δ) : 0.87 (6H, d, J=7Hz), 1.49 (9H, s), 1.81 (1H, m), 2.41 (2H, d, J=7Hz), 3.90 (3H, s), 4.84 (2H, s), 7.02 (4H, s), 7.3-7.5 (2H, m), 8.4-8.5 (2H, m)

(3) Methyl 3-[N-benzoyl-N-(4-isobutylphenyl)aminomethyl]-benzoate
NMR ($CDCl_3$, δ) : 0.80 (6H, d, J=7Hz), 1.74 (1H, m), 2.35 (2H, d, J=7Hz), 3.89 (3H, s), 5.17 (2H, s), 6.79 (2H, d, J=8Hz), 6.91 (2H, d, J=8Hz), 7.1-7.3 (3H, m), 7.3-7.5 (3H, m), 7.59 (1H, d, J=7.5Hz), 7.9-8.0 (2H, m)

Preparation 19

Sulfuric acid (2 ml) was added to a mixture of 2,3-dimethylphenol (0.81 g) and 2-ethoxycarbonyl-4-isobutylcyclohexanone (1.0 g) at 0°C. The mixture was stirred at room temperature for 16 hours, poured into ice water and partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (50 g) using a mixture of n-hexane and 2.5-10% ethyl acetate as the eluent. Appropriate fractions were combined and evaporated. The residue was crystallized with n-hexane to give 3,4-dimethyl-8-isobutyl-7,8,9,10-tetrahydro-6H-dibenzo[b,d]pyran-6-one (0.66 g) as a colorless solid.

mp : 92-93°C

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7Hz), 1.3-1.5 (3H, m), 1.7-2.2 (4H, m), 2.37 (6H, s), 2.6-3.1 (3H, m), 7.07 (1H, d, J=8Hz), 7.31 (1H, d, J=8Hz)

Preparation 20

To a solution of 3,4-dimethyl-8-isobutyl-7,8,9,10-tetrahydro-6H-dibenzo[b,d]pyran-6-one (0.22 g) in tetrahydrofuran (10 ml) was added 3M-methylmagnesium bromide in ether (1.5 ml) at 0°C. The mixture was refluxed for 1 hour and acidified with 7% hydrochloric acid at 0°C. The mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and dried over magnesium sulfate. The solvent was removed in vacuo to give 8-isobutyl-7,8,9,10-tetrahydro-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyrane (223 mg) as a colorless oil.

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7Hz), 1.1-1.4 (3H, m), 1.29 (3H, s), 1.41 (3H, s), 1.6-2.0 (4H, m), 2.0-2.2 (1H, m), 2.12 (3H, s), 2.24 (3H, s), 2.3-2.5 (2H, m), 6.67 (1H, d, J=8Hz), 6.85 (1H, d, J=8Hz)

Preparation 21

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (0.38 g) was added to a solution of 8-isobutyl-7,8,9,10-tetrahydro-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyrane (0.23 g) in toluene (5 ml). After the mixture was stirred at room temperature for 1.5 hours, allowed to stir at 100°C for 1 hour. The mixture was washed with diluted hydrochloric acid, diluted aqueous sodium bicarbonate solution and water. The solution was dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel using a mixture of n-hexane and 3% ethyl acetate as the eluent. Appropriate fractions were combined and evaporated to give 8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyrane (184 mg) as a colourless solid.

mp : 39-40°C

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7Hz), 1.61 (6H, s), 1.87 (1H, m), 2.18 (3H, s), 2.28 (3H, s), 2.49 (2H, d, J=7Hz), 6.81 (1H, d, J=8Hz), 6.98 (1H, d, J=1Hz), 7.10 (1H, dd, J=1Hz, 8Hz), 7.45 (1H, d, J=8Hz), 7.60 (1H, d, J=8Hz)

Preparation 22

To a solution of 8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyrane (0.18 g) and dichloromethyl methyl ether (0.11 ml) in benzene (5 ml) was added 1M solution of titanium (IV) chloride in dichloromethane (1.2 ml) at 0°C. The mixture was stirred at room temperature for 30 minutes and partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (12 g) using a mixture of n-hexane and 3-5% ethyl acetate as a eluent. Appropriate fractions were combined and evaporated to give

2-formyl-8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]-pyrane (180 mg) as a colourless oil.

NMR ($CDCl_3$, δ) : 0.94 (6H, d, J=7Hz), 1.66 (6H, s), 1.89 (1H, m), 2.24 (3H, s), 2.51 (2H, d, J=7Hz), 2.62 (3H, s), 7.01 (1H, d, J=1Hz), 7.16 (1H, dd, J=1Hz, 8Hz), 7.72 (1H, d, J=8Hz), 8.08 (1H, s), 10.27 (1H, s)

Preparation 23

To a solution of 2-formyl-8-isobutyl-3,4,6,6-tetramethyl dibenzo[b,d]pyrane (286 mg) in acetone (2 ml) was added 2N Jone's reagent (2.5 ml) at 0°C. The mixture was stirred at 0°C for 4 hours and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The resulting solid was collected, washed with n-hexane and dried to give 8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]pyrane-2-carboxylic acid (261 mg).

mp.: 179-180°C

NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7Hz), 1.65 (6H, s), 1.7-2.0 (1H, m), 2.26 (3H, s), 2.50 (2H, d, J=7Hz), 2.62 (3H, s), 7.01 (1H, d, J=1Hz), 7.15 (1H, dd, J=1Hz, 8Hz), 7.70 (1H, d, J=8Hz), 8.34 (1H, s)

Preparation 24

A mixture of 3-bromo-4,5-dimethylbenzyl 3-isobutylphenyl ether (2.00 g), magnesium (280 mg) and 1,2-dibromoethane (540 mg) in tetrahydrofuran (20 ml) was refluxed for 2 hours, and then allowed to cool to 25°C. After addition of dry ice (2 g), the reaction mixture was poured into a mixture of ether and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by

recrystallization from a mixture of ethyl acetate and hexane to give 2,3-dimethyl-5-(3-isobutylphenoxymethyl)-benzoic acid (1.56 g) as colorless crystals.

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.65-1.98 (1H, m), 2.37 (3H, s), 2.45 (2H, d, J=7.5Hz), 2.55 (3H, s), 5.02 (2H, s), 6.72-6.85 (3H, m), 7.18 (1H, dd, J=6Hz, 8Hz), 7.45 (1H, d, J=1Hz), 7.90 (1H, d, J=1Hz)

Preparation 25

The following compounds were obtained according to a similar manner to that of Preparation 24.

(1) 2,3-Dimethyl-4-[1-(4-isobutylphenyl)ethoxy]benzoic acid

mp : 139°C

NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7Hz), 1.65 (3H, d, J=6Hz), 1.84 (1H, m), 2.30 (3H, s), 2.45 (2H, d, J=7Hz), 2.57 (3H, s), 5.37 (1H, q, J=6Hz), 6.61 (1H, d, J=10Hz), 7.10 (2H, d, J=8Hz), 7.25 (2H, d, J=8Hz), 7.75 (1H, d, J=10Hz)

(2) 3-[2-(4-Isobutylphenyl)-1-propenyl]benzoic acid

mp : 118-120°C

NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7Hz), 1.90 (1H, m), 2.29 (3H, d, J=1Hz), 2.50 (2H, d, J=7Hz), 6.86 (1H, d, J=1Hz), 7.17 (2H, d, J=8Hz), 7.46 (2H, d, J=8Hz), 7.4-7.6 (1H, m), 7.60 (1H, d, J=7.5Hz), 8.00 (1H, d, J=7.5Hz), 8.12 (1H, s)

(3) 3-[2,2-Bis(4-isobutylphenyl)ethyl]benzoic acid

mp : 112-113°C

NMR ($CDCl_3$, δ) : 0.86 (12H, d, J=7Hz), 1.78 (2H, m), 2.36 (4H, d, J=7Hz), 3.20 (2H, d, J=7.5Hz), 4.07 (1H, t, J=7.5Hz), 7.2-6.7 (10H, m), 7.8-7.6 (2H, m)

(4) 4-[2,2-Bis(4-isobutylphenyl)ethyl]benzoic acid
mp : 181-182°C
NMR ($CDCl_3$, δ) : 0.90 (12H, d, J=7.5Hz), 1.7-2.0 (2H, m), 2.41 (4H, d, J=7.5Hz), 3.39 (2H, d, J=7.5Hz), 4.16 (1H, t, J=7.5Hz), 6.95-7.2 (10H, m), 7.88 (2H, d, J=7.5Hz)

(5) 3-[Bis(4-isobutylphenyl)methylthio]benzoic acid
NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=6Hz), 1.82 (2H, m), 2.42 (4H, d, J=6Hz), 5.52 (1H, s), 7.07 (2H, d, J=8Hz), 7.15-7.45 (6H, m), 7.82 (1H, d, J=8Hz), 7.95 (1H, s)

(6) 2,3-Dimethyl-5-(4-isobutylphenoxymethyl)benzoic acid
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.68-1.94 (1H, m), 2.37 (3H, s), 2.51 (2H, d, J=7.5Hz), 2.55 (3H, s), 5.00 (2H, s), 6.88 (2H, d, J=8Hz), 7.07 (2H, d, J=8Hz), 7.45 (1H, d, J=1Hz), 7.88 (1H, d, J=1Hz)

Preparation 26

A 1.6N solution of butyl lithium in hexane (9.7 ml) was added to a suspension of isopropyl triphenylphosphonium iodide (5.82 g) in tetrahydrofuran (50 ml) at 0°C. The reaction mixture was allowed to warm up to 25°C and stirred at the same temperature for 1 hour. A solution of methyl 3-(3-formylphenoxymethyl)benzoate (2.8 g) in tetrahydrofuran (20 ml) was added to the mixture at 0°C. The reaction mixture was stirred at 0°C for 30 minutes and the solvent was evaporated off. The residue was quenched with 1N hydrochloric acid and the mixture was extracted with ether. The extract was washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel (40 g) eluting with 10%

ethyl acetate in hexane to give methyl 3-[3-(2-methyl-1-propenyl)phenoxymethyl]benzoate (2.55 g) as an oil.

NMR ($CDCl_3$, δ) : 1.82 (3H, d, J=1Hz), 1.87 (3H, d, J=1Hz), 3.92 (3H, s), 6.22 (1H, t, J=1Hz), 6.77-6.88 (3H, m), 7.23 (1H, t, J=4Hz), 7.45 (1H, t, J=4Hz), 7.63 (1H, dd, J=1Hz, 4Hz), 8.00 (1H, dd, J=1Hz, 4Hz), 8.11 (1H, d, J=1Hz)

Preparation 27

The following compounds were obtained according to a similar manner to that of Preparation 26.

(1) Methyl 3-[4-(3-methyl-1-butenyl)phenoxymethyl]-benzoate

NMR ($CDCl_3$, δ) : 1.06 (6H, d, J=4Hz), 2.89 (1H, m), 3.94 (3H, s), 5.11 (2H, s), 5.39 (1H, dd, J=6Hz, 7Hz), 6.23 (1H, d, J=7Hz), 6.83 (2H, d, J=5Hz), 7.22 (2H, d, J=5Hz), 7.47 (1H, t, J=5Hz), 7.66 (1H, dd, J=1Hz, 5Hz), 8.03 (1H, dd, J=1Hz, 5Hz), 8.13 (1H, t, J=1Hz)

(2) Methyl 3-[2-(2-methyl-1-propenyl)phenoxymethyl] benzoate

NMR ($CDCl_3$, δ) : 1.82 (3H, d, J=1.5Hz), 1.92 (3H, d, J=1.5Hz), 3.93 (3H, s), 5.11 (2H, s), 6.93 (1H, s), 6.82-7.00 (2H, m), 7.10-7.25 (2H, m), 7.44 (1H, t, J=8Hz), 7.63 (1H, d, J=8Hz), 7.99 (1H, d, J=8Hz), 8.10 (1H, s)

Preparation 28

A mixture of methyl 3-[4-(3-methyl-1-butenyl)-phenoxymethyl]benzoate (1.85 g), 10% palladium on activated carbon (185 mg) in tetrahydrofuran (20 ml) was shaken under hydrogen atmosphere (4 atm) for 1 hour.

The mixture was filtered and the filtrate was evaporated in vacuo to give methyl 3-(4-isopentylphenoxymethyl)-benzoate (1.85 g) as an oil.

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=4Hz), 1.40-1.70 (3H, m), 2.56 (2H, dd, J=4Hz, 5Hz), 3.92 (3H, s), 5.08 (2H, s), 6.88 (2H, d, J=5Hz), 7.08 (2H, d, J=5Hz), 7.46 (1H, t, J=5Hz), 7.65 (1H, dd, J=1Hz, 5Hz), 8.00 (1H, dd, J=1Hz, 5Hz), 8.12 (1H, t, J=1Hz)

Preparation 29

The following compounds were obtained according to a similar manner to that of Preparation 28.

(1) Methyl 3-(3-isobutylphenoxymethyl)benzoate

NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=4Hz), 1.86 (1H, m), 2.44 (2H, d, J=4Hz), 3.91 (3H, s), 5.08 (2H, s), 6.75-6.80 (3H, m), 7.18 (1H, dd, J=4Hz, 5Hz), 7.45 (1H, t, J=4Hz), 7.63 (1H, dd, J=1Hz, 4Hz), 8.00 (1H, dd, J=1Hz, 4Hz), 8.12 (1H, t, J=1Hz)

(2) 4-Isobutylphenyl phenyl ether

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7Hz), 1.84 (1H, m), 2.45 (2H, d, J=7Hz), 6.9-7.2 (7H, m), 7.2-7.4 (2H, m)

(3) Methyl 3-(2-isobutylphenoxymethyl)benzoate

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7Hz), 1.88-2.10 (1H, m), 2.55 (2H, d, J=7.5Hz), 3.92 (3H, s), 5.10 (2H, s), 6.82-6.98 (2H, m), 7.08-7.18 (2H, m), 7.46 (1H, t, J=8Hz), 7.64 (1H, d, J=8Hz), 8.00 (1H, d, J=8Hz), 8.12 (1H, s)

Preparation 30

n-Butyl lithium (1.6 M solution in hexane) (6 ml) was

added to a solution of bis(4-isobutylphenyl)methane (2.25 g) in tetrahydrofuran (20 ml). The mixture was stirred at room temperature for 5 hours and cooled at 0°C. To the mixture was added a solution of 4-bromobenzylbromide (2.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at 0°C for 30 minutes and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (100 g) using n-hexane as the eluent. Appropriate fractions were combined and evaporated to give 1,1-bis(4-isobutylphenyl)-2-(4-bromophenyl)ethane (1.57 g) as a colourless oil.

NMR ($CDCl_3$, δ) : 0.85 (12H, d, J=7.5Hz), 1.81 (2H, m), 2.41 (4H, d, J=7Hz), 3.25 (2H, d, J=7.5Hz), 4.08 (1H, t, J=7.5Hz), 6.81 (2H, d, J=8Hz), 7.00 (4H, d, J=8Hz), 7.24 (2H, d, J=8Hz), 7.07 (4H, d, J=8Hz)

Preparation 31

The following compound was obtained according to a similar manner to that of Preparation 30.

1,1-Bis(4-isobutylphenyl)-2-(3-bromophenyl)ethane

NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.82 (2H, m), 2.41 (4H, d, J=7Hz), 3.27 (2H, d, J=7.5Hz), 4.09 (1H, t, J=7.5Hz), 6.85 (1H, d, J=7.5Hz), 7.3-7.0 (11H, m)

Preparation 32

A mixture of bis(4-isobutylphenyl)methyl acetate (12.64 g) and 10% palladium on carbon (2 g) in acetic acid (100 ml) was shaken under hydrogen atmosphere (3 atm) at room temperature for 21 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in ethyl acetate and washed with saturated

aqueous sodium bicarbonate solution and water. The solution was dried over magnesium sulfate and evaporated. The residual oil was distillated under reduced pressure to give bis(4-isobutylphenyl)methane (9.97 g) as a colourless oil.

bp : 150-155°C/0.2 mmHg

NMR ($CDCl_3$, δ) : 0.89 (12H, d, J=7Hz), 1.84 (2H, m), 2.43 (4H, d, J=7Hz), 3.92 (2H, s), 7.07 (8H, m)

Preparation 33

Acetic anhydride (20 ml) was added to a solution of bis(4-isobutylphenyl)methanol (11.07 g) in pyridine (40 ml). The mixture was stirred at room temperature for 5 hours and partitioned between ethyl acetate and water. The organic layer was washed with 7% hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and water. The solution was dried over magnesium sulfate and evaporated to give bis(4-isobutylphenyl)methyl acetate (12.64 g) as a colourless oil.

NMR ($CDCl_3$, δ) : 0.89 (12H, d, J=7Hz), 1.84 (2H, m), 2.15 (3H, s), 2.44 (4H, d, J=7Hz), 6.85 (1H, s), 7.23 (4H, d, J=8Hz)

Preparation 34

To a solution of sodium hydroxide (4.71 g) and bromine (2 ml) in water (60 ml) was added a solution of 4-(4-isobutylphenoxy)acetophenone (3.29 g) in 1,4-dioxane (90 ml). The mixture was stirred at 0°C for 2 hours and partitioned between ethyl acetate and 7% hydrochloric acid. The organic layer was washed with water and saturated aqueous sodium thiosulfate solution, dried over magnesium sulfate and evaporated. The residue was washed with n-hexane to give 4-(4-isobutylphenoxy)benzoic acid (2.60 g) as a white powder.

mp : 128°C

NMR ($CDCl_3$, δ) : 0.94 (6H, d, J=7Hz), 1.87 (1H, m), 2.50 (2H, d, J=7Hz), 7.00 (4H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 8.06 (2H, d, J=8Hz)

Preparation 35

Acetyl chloride (0.94 ml) was added to a suspension of aluminum chloride (1.76 g) in dichloromethane (15 ml) at 3°C. The mixture was stirred at 3°C for 15 minutes. To the mixture was added a solution of 4-isobutylphenyl phenyl ether (2.67 g) in dichloromethane (15 ml). The mixture was stirred at 0°C for 1 hour and poured into 7% hydrochloric acid. The organic layer was washed with water, dried over magnesium sulfate and evaporated to give 4-(4-isobutylphenoxy)acetophenone (3.30 g) as a colourless oil.

NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7Hz), 1.86 (1H, m), 2.50 (2H, d, J=7Hz), 2.57 (3H, s), 6.98 (4H, d, J=8Hz), 7.16 (2H,, d, J=8Hz), 7.94 (2H, d, J=8Hz)

Preparation 36

To a solution of dibenzyl 4,4'-biphenyldicarboxylate (4.23 g) in 1,4-dioxane (100 ml) was added 0.6N aqueous barium hydroxide solution (17 ml). The mixture was stirred at room temperature for 3 days. The resulting precipitate was collected by filtration and washed with 7% hydrochloric acid to give benzyl hydrogen 4,4'-diphenyldicarboxylate (3.21 g) as a white powder.

NMR (DMSO-d_6, δ) : 5.40 (2H, s), 7.3-7.6 (5H, m), 7.84 (2H, d, J=9Hz), 7.92 (2H, d, J=9Hz), 8.07 (2H, d, J=9Hz), 8.12 (2H, d, J=9Hz)

Preparation 37

To a suspension of sodium hydride (60% dispersion in mineral oil) (0.13 g) in tetrahydrofuran (10 ml) was added

a solution of phenyl 3-(4-isobutylbenzoyl)aminobenzoate (1.0 g) in tetrahydrofuran (10 ml). The mixture was stirred at 0°C for 15 minutes. Methyl iodide (0.95 g) was added to the mixture. The mixture was stirred at 0°C for 45 minutes and partitioned between ethyl acetate and diluted hydrochloric acid. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (20 g) using chloroform as the eluent. Appropriate fractions were combined and evaporated to give phenyl 3-[N-(4-isobutylbenzoyl)-N-methylamino]benzoate (0.51 g) as a colourless foam.

NMR ($CDCl_3$, δ) : 0.82 (6H, d, J=6Hz), 1.7-1.9 (1H, m), 2.42 (2H, d, J=6.5Hz), 3.55 (3H, s), 6.94 (2H, d, J=8.5Hz), 7.1-7.5 (9H, m), 7.9-8.0 (2H, m)

Preparation 38

4-Isobutylbenzoyl chloride (0.20 g) was added to an ice cooling solution of phenyl 3-aminobenzoate (0.21 g) in dichloromethane (10 ml). After pyridine (0.08 g) was added to the mixture, the mixture was allowed to stir at room temperature for 45 minutes. The mixture was poured into diluted hydrochloric acid. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (10 g) using a mixture of n-hexane and ethyl acetate (4:1) as the eluent. Appropriate fractions were combined and evaporated to give phenyl 3-(4-isobutylbenzoyl)aminobenzoate (0.33 g) as a colourless foam.

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=6Hz), 1.91 (1H, m), 2.53 (2H, d, J=7Hz), 7.1-7.3 (4H, m), 7.3-7.6 (3H, m), 7.81 (2H, d, J=8Hz), 7.9-8.3 (4H, m)

Preparation 39

To a suspension of sodium hydride (60% dispersion in mineral oil) (0.15 g) in tetrahydrofuran (5 ml) was added a solution of methyl 3-[N-(4-isobutylphenyl)carbamoyl]-benzoate (0.75 g) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 1 hour. 4-Isobutylbenzyl chloride (0.53 g) was added to the mixture. The mixture was refluxed for 65 hours and partitioned between ethyl acetate and 7% hydrochloric acid. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (50 g) using a mixture of n-hexane and ethyl acetate (4:1) as the eluent. Appropriate fractions were combined and evaporated to give methyl 3-[N-(4-isobutylbenzyl)-N-(4-isobutylphenyl)-carbamoyl]benzoate (0.38 g) as a colorless foam.

NMR ($CDCl_3$, δ) : 0.77 (6H, d, J=7Hz), 0.88 (6H, d, J=7Hz), 1.6-2.0 (2H, m), 2.34 (2H, d, J=7Hz), 2.45 (2H, d, J=7Hz), 3.84 (3H, s), 5.08 (2H, s), 6.78 (2H, d, J=8Hz), 6.89 (2H, d, J=8Hz), 7.06 (2H, d, J=8Hz), 7.20 (2H, d, J=8Hz), 7.21 (1H, t, J=7.5Hz), 7.48 (1H, dt, J=2Hz, 7.5Hz), 7.89 (1H, dt, J=2Hz, 7.5Hz), 8.01 (1H, t, J=2Hz)

Preparation 40

Trifluoroacetic acid (10 ml) was added to a solution of methyl 3-[N-t-butoxycarbonyl-N-(4-isobutylphenyl)-aminomethyl]benzoate (1.5 g) in dichloromethane (10 ml). The mixture was stirred at room temperature for 2 hours and evaporated. The residue was dissolved in dichloromethane (50 ml), washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and evaporated. The residue was dissolved in tetrahydrofuran (15 ml). To the solution was added 4-isobutylbenzyl chloride (2.48 g) and potassium

tert-butoxide (1.24 g). The mixture was stirred at room temperature for 5 hours, poured into ice water and dissolved in 1N-sodium hydroxide aqueous solution. The solution was washed with diethyl ether, acidified with diluted hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (70 g) using a mixture of chloroform and 10% methanol as the eluent. Appropriate fractions were combined and evaporated to give 3-[N-(4-isobutylbenzyl)-N-(4-isobutylphenyl)aminomethyl]benzoic acid (116 mg) as a colorless foam.

NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7Hz), 0.90 (6H, d, J=7Hz), 1.6-2.0 (2H, m), 2.35 (2H, d, J=7Hz), 2.45 (2H, d, J=7Hz), 4.62 (2H, s), 4.64 (2H, s), 6.67 (2H, d, J=8Hz), 6.95 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.17 (2H, d, J=8Hz), 7.3-7.6 (2H, m), 7.9-8.1 (2H, m)

Preparation 41

Thionyl chloride (4.5 ml) was added to a solution of 4-(1-hydroxy-4-isobutylcyclohexyl)benzyl methyl ether (2.24 g) in pyridine (45 ml) at 5°C over 20 minutes. After stirred at 5°C for 2.5 hours, the reaction mixture was quenched with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel (100 g) eluting with a mixture of ethyl acetate and hexane to give 4-(4-isobutyl-1-cyclohexenyl)benzyl methyl ether (1.52 g) as an oil.

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7Hz), 1.18 (2H, t, J=7Hz), 1.24-1.44 (1H, m), 1.60-1.98 (4H, m), 2.20-2.50 (3H, m), 3.40 (3H, s), 4.43 (2H, s),

6.06-6.12 (1H, m), 7.27 (2H, d, J=8Hz), 7.38 (2H, d, J=8Hz)

Preparation 42

A mixture of 4-(4-isobutyl-1-cyclohexenyl)benzyl methyl ether (1.37 g) and 2,3-dichloro-5,6-dicyclo-1,4-benzoquinone (6.01 g) in toluene (50 ml) was refluxed for 5 hours. The reaction mixture was quenched with 1N hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel (100 g) eluting with a mixture of ethyl acetate and hexane (1:50) to give 4-(4-isobutylphenyl)benzaldehyde (820 mg) as an oil.

NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.75-1.98 (1H, m), 2.46 (2H, d, J=7.5Hz), 7.20 (2H, d, J=8Hz), 7.48 (2H, d, J=8Hz), 7.68 (2H, d, J=8Hz), 7.86 (2H, d, J=8Hz), 9.98 (1H, s)

Preparation 43

A solution of 4-(4-isobutylphenyl)benzaldehyde (200 mg) in acetone (2 ml) was added to a solution of 2N Jones reagent (0.9 ml) in acetone (5 ml) at 0°C over 10 minutes. The reaction mixture was poured into a mixture of ice-water and ethyl acetate. The organic layer was separated, washed with water, dried over magnesium sulfate, and evaporated to give 4-(4-isobutylphenyl)-benzoic acid (195 mg) as an oil.

NMR ($CDCl_3$, δ) : 0.95 (6H, d, J=7.5Hz), 1.80-2.0 (1H, m), 2.54 (2H, d, J=7.5Hz), 7.26 (2H, d, J=8Hz), 7.57 (2H, d, J=8Hz), 7.70 (2H, d, J=8Hz), 8.18 (2H, d, J=8Hz)

Preparation 44

A mixture of 3-cyano-4'-isobutylstilbene (875 mg) and

3NHCl (15 ml) in formic acid (50 ml) was heated under reflux with stirring for 3 days. The reaction mixture was evaporated under reduced pressure and extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate and evaporated under reduced pressure to give a residue which was crystallized from isopropyl ether to afford 4'-isobutylstilbene-3-carboxylic acid (512 mg).

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7.5Hz), 1.79 (1H, m), 2.49 (2H, d, J=7.5Hz), 7.05-7.25 (4H, m), 7.39-7.50 (3H, m), 7.70 (1H, m), 7.95 (1H, m), 8.22 (1H, m)

Preparation 45

To a suspension of 3-aminobenzoic acid (1.37 g) and potassium carbonate (7.0 g) in dimethylformamide (50 ml) was added 4-isobutylbenzyl chloride (7.3 g). The mixture was stirred for 4 hours at 50°C and poured into diluted hydrochloric acid (200 ml). The organic layer was extracted with ethyl acetate (30 ml) and washed with water. The solution was dried over magnesium sulfate and the solvent was removed in vacuo. The residue was purified by a column chromatography of silica gel to give colorless oil of 4-isobutylbenzyl 3-[bis(4-isobutylbenzyl)amino]benzoate (1.56 g).

NMR ($CDCl_3$, δ) : 0.6-0.8 (18H, m), 1.5-1.8 (3H, m), 2.20 (4H, d, J=7.5Hz), 2.23 (2H, d, J=7.5Hz), 4.37 (4H, s), 5.00 (2H, s), 6.6-6.7 (1H, m), 6.8-7.2 (14H, m), 7.2-7.3 (1H, m)

Preparation 46

To a mixture of methyl 4-hydroxybebzoate (1.52 g) and potassium carbonate (3.0 g) in dimethylformamide (10 ml) was added 4-isobutylbenzyl chloride (2.0 g). After stirring for 6 hours at 50°C, the mixture was poured into

diluted hydrochloric acid (120 ml). The organic layer was extracted with ethyl acetate (50 ml) and washed with water (30 ml x 2). The solution was dried over magnesium sulfate and the solvent was removed in vacuo. The residue was crystallized with n-hexane to give a white solid of methyl 4-(4-isobutylbenzyloxy)benzoate (1.98 g).

NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.7-2.1 (1H, m), 2.50 (2H, d, J=7.5Hz), 3.87 (3H, s), 5.05 (2H, s), 7.00 (2H, d, J=10Hz), 7.18 (2H, d, J=7.5Hz), 7.33 (2H, d, J=7.5Hz), 8.00 (2H, d, J=10Hz)

Preparation 47

The following compounds were obtained according to a similar manner to that of Preparation 46.

(1) 4-Bromo-2,3-dimethylphenyl-1-(4-isobutylphenyl)ethyl ether

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.62 (3H, d, J=6Hz), 1.84 (1H, m), 2.29 (3H, s), 2.36 (3H, s), 2.44 (2H, d, J=7.5Hz), 5.22 (1H, q, J=6Hz), 6.45 (1H, d, J=9Hz), 7.09 (2H, d, J=7.5Hz), 7.17 (1H, d, J=9Hz), 7.23 (2H, d, J=7.5Hz)

(2) Methyl 3-[1-(4-isobutylphenyl)ethoxy]benzoate

NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=4Hz), 1.64 (3H, d, J=4Hz), 1.82 (1H, m), 2.43 (2H, d, J=4Hz), 3.87 (3H, s), 5.34 (1H, q, J=4Hz), 7.00-7.15 (3H, m), 7.20-7.35 (3H, s), 7.50-7.60 (2H, m)

(3) Methyl 3-(3-formylphenoxymethyl)benzoate

NMR ($CDCl_3$, δ) : 3.92 (3H, s), 5.19 (2H, s), 7.26 (1H, m), 7.2-7.4 (4H, m), 7.64 (1H, dd, J=1Hz, 5Hz), 8.01 (1H, dd, J=1Hz, 5Hz), 8.14 (1H, t, J=1Hz)

(4) Methyl 3-(3,4-dichlorophenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 3.90 (3H, s), 5.05 (2H, s), 7.15 (1H, dd, J=2.5Hz, 8Hz), 7.27 (1H, dd, J=2.5Hz, 8Hz), 7.36 (1H, t, J=8Hz), 7.55 (1H, d, J=2.5Hz), 7.62 (1H, s), 7.69 (1H, d, J=8Hz)

(5) Methyl 3-(methoxymethoxy)benzoate
NMR ($CDCl_3$, δ) : 3.50 (3H, s), 3.90 (3H, s), 5.22 (2H, s), 7.23 (1H, m), 7.34 (1H, t, J=6Hz), 7.7-7.8 (2H, m)

(6) Bis(4-isobutylphenyl)(3-bromophenylthio)methane
NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=6Hz), 1.84 (2H, m), 2.44 (4H, d, J=6Hz), 5.48 (1H, s), 6.96-7.15 (6H, m), 7.20-7.35 (6H, m)

(7) Methyl 3-(3,4-dichlorobenzyloxy)benzoate
NMR ($CDCl_3$, δ) : 3.90 (3H, s), 5.05 (2H, s), 7.15 (1H, dd, J=2.5Hz, 8Hz), 7.36 (1H, t, J=8Hz), 7.46 (1H, d, J=8Hz), 7.55 (1H, d, J=2.5Hz), 7.62 (1H, broad s), 7.69 (1H, d, J=8Hz)

(8) Methyl 3-(3-bromophenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 3.92 (3H, s), 5.09 (2H, s), 6.85-6.95 (1H, m), 7.05-7.65 (4H, m), 7.95-8.10 (3H, m)

(9) 3-(Isopropoxy)phenol
NMR ($CDCl_3$, δ) : 1.32 (6H, d, J=7.5Hz), 4.40-4.60 (1H, m), 5.18 (1H, s), 6.35-6.55 (3H, m), 7.12 (1H, t, J=8.0Hz)

(10) Methyl 3-[3-(isopropoxy)phenoxymethyl]benzoate
NMR ($CDCl_3$, δ) : 1.35 (6H, d, J=7.5Hz), 3.93 (3H, s), 4.43-4.65 (1H, m), 5.08 (2H, s), 6.45-6.62

(3H, m), 7.10-7.20 (1H, m), 7.45 (1H, t, J=8Hz), 7.65 (1H, d, J=8Hz), 8.01 (1H, d, J=8.0Hz), 8.10 (1H, broad s)

(11) Methyl 3-(4-isobutylphenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7Hz), 1.70-1.94 (1H, m), 2.41 (2H, d, J=8Hz), 3.92 (3H, s), 5.08 (2H, s), 6.90 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.46 (1H, t, J=8Hz), 7.66 (1H, dd, J=1Hz, 8Hz), 8.00 (1H, dd, J=1Hz, 8Hz), 8.12 (1H, t, J=1Hz)

(12) Methyl 4-(4-propylphenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 0.92 (3H, t, J=7.5Hz), 1.50-1.70 (2H, m), 2.53 (2H, t, J=7.5Hz), 3.92 (3H, s), 5.12 (2H, s), 6.88 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.50 (2H, d, J=8Hz), 8.06 (2H, d, J=8Hz)

(13) 3-Bromo-4,5-dimethylbenzyl 3-isobutylphenyl ether
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.75-1.98 (1H, m), 2.33 (3H, s), 2.37 (3H, s), 2.44 (2H, d, J=7.5Hz), 4.93 (2H, s), 6.72-6.84 (3H, m), 7.14-7.24 (2H, m), 7.50 (1H, d, J=1Hz)

(14) 3-Bromo-4,5-dimethylbenzyl 4-isobutylphenyl ether
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.70-1.94 (1H, m), 2.34 (3H, s), 2.36 (3H, s), 2.41 (2H, d, J=7.5Hz), 4.92 (2H, s), 6.88 (2H, d, J=8Hz), 7.06 (2H, d, J=8Hz), 7.15 (1H, d, J=1Hz), 7.48 (1H, d, J=1Hz)

(15) Methyl 3-(2-formylphenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 3.93 (3H, s), 5.22 (2H, s), 6.98-7.12 (2H, m), 7.43-7.72 (3H, m), 7.88 (1H, dd, J=2.5Hz, 8Hz), 8.05 (1H, d, J=8Hz), 8.12 (1H, broad s), 10.58 (1H, s)

Preparation 48

To a solution of methyl 4-(4-isobutylbenzyloxy)-benzoate (1.90 g) in 1,4-dioxane (10 ml) was added 1N-sodium hydroxide (10 ml). The mixture was stirred for 3 hours and poured into diluted hydrochloric acid (110 ml). The organic layer was extracted with ethyl acetate (30 ml) and washed with water (30 ml x 3). The solution was dried over magnesium sulfate and the solvent was removed in vacuo. The residue was crystallized with n-hexane to give a white solid of 4-(4-isobutylbenzyloxy)benzoic acid (1.78 g).

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J-7.5Hz), 1.70-2.0 (1H, m), 2.50 (2H, d, J=7.5Hz), 5.08 (2H, s), 7.02 (2H, d, J=10Hz), 7.18 (2H, d, J=7.5Hz), 7.35 (2H, d, J=7.5Hz), 8.06 (2H, d, J=10Hz)

Preparation 49

The following compounds were obtained according to a similar manner to that of Preparation 48.

(1) 3-[Bis(4-isobutylbenzyl)amino]benzoic acid

NMR ($CDCl_3$, δ) : 0.90 (12H, d, J=7.5Hz), 1.7-2.0 (2H, m), 2.45 (4H, d, J=7.5Hz), 4.65 (4H, s), 6.9-7.0 (1H, m), 7.10 (8H, dd, J=7.5Hz), 7.23 (1H, t, J=7.5Hz), 7.42 (1H, d, J=7.5Hz), 7.53 (1H, s)

(2) 3-[1-(4-Isobutylphenyl)ethoxy]benzoic acid

NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=4Hz), 1.64 (3H, d, J=4Hz), 1.82 (1H, m), 2.43 (2H, d, J=4Hz), 5.34 (1H, q, J=4Hz), 7.00-7.15 (3H, m), 7.20-7.35 (3H, m), 7.50-7.60 (2H, m)

(3) 3-(3-Isobutylphenoxymethyl)benzoic acid

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=8Hz), 1.76-2.00 (1H,

m), 2.46 (2H, d, J=8Hz), 5.10 (2H, s), 6.73-6.85 (3H, m), 7.20 (1H, dd, J=8Hz, 10Hz), 7.50 (1H, t, J=8Hz), 7.72 (1H, dd, J=1Hz, 8Hz), 8.09 (1H, dd, J=1, 8Hz), 8.19 (1H, t, J=1Hz)

(4) 3-(4-Isopentylphenoxymethyl)benzoic acid
NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=4Hz), 1.40-1.70 (3H, m), 2.57 (2H, dd, J=4Hz, 5Hz), 5.12 (2H, s), 6.90 (2H, d, J=5Hz), 7.12 (2H, d, J=5Hz), 7.51 (1H, t, J=5Hz), 7.72 (1H, dd, J=1Hz, 5Hz), 8.08 (1H, dd, J=1Hz, 5Hz), 8.19 (1H, t, J=1Hz)

(5) 4,5-Dimethyl-3-[1-(4-isobutylphenyl)ethoxy]benzoic acid
NMR ($CDCl_3$, δ) : 0.80 (6H, d, J=7.5Hz), 1.54 (3H, d, J=7.5Hz), 1.62-1.92 (1H, m), 2.20 (3H, s), 2.22 (3H, s), 2.38 (2H, d, J=7.5Hz), 5.30 (1H, q, J=7.5Hz), 7.02 (2H, d, J=8Hz), 7.12-7.33 (3H, m), 7.41 (1H, s)

(6) 3-(3,4-Dichlorophenoxymethyl)benzoic acid
NMR ($CDCl_3$, δ) : 5.04 (2H, s), 7.17 (1H, dd, J=2.5Hz, 8Hz), 7.28 (1H, dd, J=2.5Hz, 8Hz), 7.37 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.55 (1H, d, J=2.5Hz), 7.65 (1H, s), 7.70 (1H, d, J=8Hz)

(7) 3-(Methoxymethoxy)benzoic acid
NMR ($CDCl_3$, δ) : 3.50 (3H, s), 5.25 (2H, s), 7.30 (1H, m), 7.40 (1H, t, J=6Hz), 7.65-7.75 (2H, m)

(8) 4-(Methoxymethoxy)benzoic acid
NMR ($CDCl_3$, δ) : 3.52 (3H, s), 5.28 (2H, s), 7.10 (2H, d, J=10Hz), 8.10 (2H, d, J=10Hz)

(9) 3-(3,4-Dichlorobenzyloxy)benzoic acid

NMR ($CDCl_3$-CD_3OD, δ) : 5.04 (2H, s), 7.17 (1H, dd, J=2.5Hz, 8Hz), 7.28 (1H, dd, J=2.5Hz, 8Hz), 7.37 (1H, t, J=8Hz), 7.45 (1H, d, J=8Hz), 7.55 (1H, d, J=2.5Hz), 7.65 (1H, broad s), 7.70 (1H, broad d, J=8Hz)

(10) 3-(3-Bromophenoxymethyl)benzoic acid
NMR ($CDCl_3$-CD_3OD, δ) : 5.10 (2H, s), 6.85-6.98 (1H, m), 7.02-7.20 (3H, m), 7.50 (1H, t, J=8Hz), 7.65 (1H, d, J=8Hz), 8.02 (1H, d, J=8Hz), 8.12 (1H, broad s)

(11) 3-[3-(Isopropoxyphenoxy)methyl]benzoic acid
NMR ($CDCl_3$, δ) : 1.33 (6H, d, J=7.5Hz), 4.42-4.65 (1H, m), 5.10 (2H, s), 6.48-6.64 (3H, m), 7.10-7.25 (1H, m), 7.52 (1H, t, J=8Hz), 7.70 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz), 8.19 (1H, broad s)

(12) 3-[N-(4-Isobutylbenzyl)-N-(4-isobutylphenyl) carbamoyl]benzoic acid
mp : 142-143°C
NMR ($CDCl_3$, δ) : 0.77 (6H, d, J=7Hz), 0.88 (6H, d, J=7Hz), 1.6-2.0 (2H, m), 2.34 (2H, d, J=7Hz), 2.45 (2H, d, J=7Hz), 5.09 (2H, s), 6.78 (2H, d, J=8Hz), 6.90 (2H, d, J=8Hz), 7.07 (2H, d, J=8Hz), 7.22 (2H, d, J=8Hz), 7.26 (1H, t, J=7.5Hz), 7.58 (1H, dt, J=2Hz, 7.5Hz), 7.94 (1H, dt, J=2Hz, 7.5Hz), 8.03 (1H, t, J=2Hz)

(13) 3-[N-(4-Isobutylbenzoyl)-N-(4-isobutylphenyl)amino-methyl]benzoic acid
mp : : 126-127°C
NMR ($CDCl_3$, δ) : 0.78 (12H, d, J=7Hz), 1.6-1.9 (2H, m), 2.34 (2H, d, J=7Hz), 2.36 (2H, d, J=7Hz),

5.18 (2H, s), 6.80 (2H, d, J=8Hz), 6.90 (2H, d, J=8Hz), 6.92 (2H, d, J=8Hz), 7.24 (2H, d, J=8Hz), 7.42 (1H, t, J=7.5Hz), 7.66 (1H, d, J=7.5Hz), 7.9-8.1 (2H, m)

(14) 3-[N-(4-Isobutylbenzoyl)-N-(3-isobutylphenyl)-aminomethyl]benzoic acid
NMR ($CDCl_3$, + CD_3OD, δ) : 0.65 (6H, d, J=7Hz), 0.81 (6H, d, J=7Hz), 1.52 (1H, m), 1.76 (1H, m), 2.25 (2H, d, J=7Hz), 2.36 (2H, d, J=7Hz), 5.19 (2H, s), 6.58 (1H, br s), 6.8-7.0 (2H, m), 6.92 (2H, d, J=8Hz), 7.09 (1H, t, J=7.5Hz), 7.26 (2H, d, J=8Hz), 7.41 (1H, t, J=7.5Hz), 7.65 (1H, d, J=7.5Hz), 7.98 (1H, d, J=7.5Hz), 8.00 (1H, br s)

(15) 3-[N-Benzoyl-N-(4-isobutylphenyl)aminomethyl]benzoic acid
NMR ($CDCl_3$, δ) : 0.79 (6H, d, J=7Hz), 1.74 (1H, m), 2.34 (2H, d, J=7Hz), 5.19 (2H, s), 6.80 (2H, d, J=8Hz), 6.91 (2H, d, J=8Hz), 7.1-7.3 (3H, m), 7.3-7.4 (2H, m), 7.42 (1H, t, J=8Hz), 7.66 (1H, d, J=8Hz), 7.98 (1H, s), 8.00 (1H, d, J=8Hz)

(16) 3-(4-Isobutylphenoxymethyl)benzoic acid
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7Hz), 1.70-1.84 (1H, m), 2.42 (2H, d, J=8Hz), 5.10 (2H, s), 6.90 (2H, d, J=8Hz), 7.06 (2H, d, J=8Hz), 7.50 (1H, t, J=8Hz), 7.72 (1H, dd, J=1Hz, 8Hz), 8.08 (1H, dd, J=1Hz, 8Hz), 8.18 (1H, t, J=1Hz)

(17) 4-(4-Propylphenoxymethyl)benzoic acid
NMR ($CDCl_3$, δ) : 0.94 (3H, t, J=7.5Hz), 1.50-1.70 (2H, m), 2.52 (2H, t, J=7.5Hz), 5.12 (2H, s), 6.90 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 8.12 (2H, d, J=8Hz)

(18) 3-(2-Isobutylphenoxymethyl)benzoic acid
NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7.5Hz), 1.85-2.10 (1H, m), 2.59 (2H, d, J=7.5Hz), 5.12 (2H, s), 6.80-6.95 (2H, m), 7.08-7.22 (2H, m), 7.50 (1H, t, J=8Hz), 7.70 (1H, d, J=8Hz), 8.09 (1H, d, J=8Hz), 8.21 (1H, s)

(19) 4-[2-(4-Isobutylphenyl)-1-propenyl]benzoic acid
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.90 (1H, m), 2.30 (3H, d, J=0.4Hz), 2.50 (2H, d, J=7.5Hz), 6.85 (1H, s), 7.18 (2H, d, J=10Hz), 7.45 (4H, d, J=10Hz), 8.12 (2H, d, J=10Hz)

Preparation 50

To a solution of 3-(3-isobutylphenoxymethyl)benzoic acid (1.75 g) in dichloromethane (20 ml) were added oxalyl chloride (0.644 ml) and dimethylformamide (2 drops) at 25°C. The reaction mixture was stirred at 25°C for 2 hours and evaporated in vacuo. The residue was dissolved in tetrahydrofuran (10 ml) and the solution was added to a solution of sodium phenolate, which was prepared with phenol (1.16 g) and sodium hydride (60% dispersion in mineral oil, 492 mg), in tetrahydrofuran (20 ml) at 25°C over 15 minutes. The mixture was quenched with 1N hydrochloric acid, and was extracted with ether. The extract was washed with water and brine, and dried over magnesium sulfate. After evaporation at the solvent, the residue was chromatographed on silica gel (40 g) eluting with a mixture of dichloromethane and hexane (1:1) to give phenyl 3-(3-isobutylphenyloxymethyl)benzoate (2.15 g) as a colorless oil.

NMR ($CDCl_3$, δ) : 1.88 (6H, d, J=4Hz), 1.86 (1H, m), 2.44 (2H, d, J=4Hz), 5.13 (2H, s), 6.72-6.87 (3H, m), 7.14-7.60 (7H, m), 7.72 (1H, dd, J=1Hz, 4Hz), 8.18 (1H, dd, J=1Hz, 4Hz), 8.28 (1H, t, J=1Hz)

Preparation 51

The following compounds were obtained according to a similar manner to that of Preparation 50.

(1) Phenyl 3-(4-isopentylphenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=4Hz), 1.4-1.7 (3H, m), 2.57 (2H, dd, J=4Hz, 5Hz), 5.12 (2H, s), 6.92 (2H, d, J=5Hz), 7.12 (2H, d, J=5Hz), 7.20-7.60 (5H, m), 7.73 (1H, dd, J=1Hz, 5Hz), 8.18 (1H, dd, J=1Hz, 5Hz), 8.29 (1H, t, J=1Hz)

(2) Phenyl 4-(4-isobutylbenzyloxy)benzoate
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.7-2.0 (1H, m), 2.50 (2H, d, J=7.5Hz), 5.10 (2H, s), 7.05 (2H, d, J=10Hz), 7.1-7.5 (9H, m), 8.17 (2H, d, J=10Hz)

(3) Phenyl 3-[bis(4-isobutylbenzyl)amino]benzoate
NMR ($CDCl_3$, δ) : 0.90 (12H, d, J=7.5Hz), 1.7-2.0 (2H, m), 2.45 (4H, d, J=7.5Hz), 4.65 (4H, s), 6.9-7.0 (1H, m), 7.0-7.5 (14H, m), 7.52 (1H, d, J=7.5Hz), 7.62 (1H, s)

(4) Phenyl 2,3-dimethyl-4-[1-(4-isobutylphenyl)ethoxy]-benzoate
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7Hz), 1.67 (3H, d, J=6Hz), 1.84 (1H, m), 2.32 (3H, s), 2.44 (2H, d, J=7Hz), 2.58 (3H, s), 5.38 (1H, q, J=6Hz), 6.66 (1H, d, J=10Hz), 7.0-7.2 (4H, m), 7.2-7.3 (3H, m), 7.3-7.5 (2H, m), 7.86 (1H, d, J=10Hz)

(5) Phenyl 3-[1-(4-isobutylphenyl)ethoxy]benzoate
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=4Hz), 1.64 (3H, d, J=4Hz), 1.82 (1H, m), 2.43 (2H, d, J=4Hz), 5.37 (3H, q, J=4Hz), 7.05-7.45 (11H, m), 7.30-7.40 (2H, m)

(6) Phenyl 4,5-dimethyl-3-[1-(4-isobutylphenyl)ethoxy]-benzoate
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.63 (3H, d, J=7.5Hz), 1.74-1.94 (1H, m), 2.30 (3H, s), 2.32 (3H, s), 2.43 (2H, d, J=7.5Hz), 5.40 (1H, q, J=7.5Hz), 7.04-7.20 (4H, m), 7.20-7.34 (3H, m), 7.34-7.48 (3H, m), 7.60 (1H, s)

(7) Phenyl 3-(3,4-dichlorophenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 5.11 (2H, s), 6.85 (1H, dd, J=2.5Hz, 10Hz), 7.11 (1H, d, J=2.5Hz), 7.12-7.62 (7H, m), 7.70 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz), 8.25 (1H, s)

(8) Phenyl 3-(methoxymethoxy)benzoate
NMR ($CDCl_3$, δ) : 3.51 (3H, s), 5.26 (2H, s), 7.2-7.5 (7H, m), 7.85-7.90 (2H, m)

(9) Phenyl 4-(methoxymethoxy)benzoate
NMR ($CDCl_3$, δ) : 3.50 (3H, s), 5.25 (2H, s), 7.12 (2H, d, J=10Hz), 7.15-7.30 (3H, m), 7.45 (2H, m), 8.15 (2H, d, J=10Hz)

(10) Phenyl 3-[bis(4-isobutylphenyl)methylthio]benzoate
NMR ($CDCl_3$, δ) : 0.92 (12H, d, J=6Hz), 1.86 (1H, m), 2.45 (4H, d, J=6Hz), 5.62 (1H, s), 7.11 (2H, d, J=8Hz), 7.15-7.50 (9H, m), 7.95 (1H, broad d, J=6Hz), 8.10 (1H, broad s)

(11) Phenyl 3-(3,4-dichlorophenylmethoxy)benzoate
NMR ($CDCl_3$, δ) : 5.10 (2H, s), 7.15-7.39 (5H, m), 7.39-7.55 (4H, m), 7.59 (1H, d, J=2.5Hz), 7.80 (1H, broad s), 7.89 (1H, d, J=8Hz)

(12) Phenyl 3-(3-bromophenoxymethyl)benzoate

NMR ($CDCl_3$, δ) : 5.12 (2H, s), 6.85-7.00 (1H, m), 7.05-7.35 (6H, m), 7.35-7.65 (3H, m), 7.70 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.25 (1H, broad s)

(13) Phenyl 3-[3-(isopropoxy)phenoxymethyl]benzoate
NMR ($CDCl_3$, δ) : 1.33 (6H, d, J=8.5Hz), 4.42-4.62 (1H, m), 5.12 (1H, s), 6.43-6.62 (3H, m), 7.10-7.34 (4H, m), 7.34-7.60 (3H, m), 7.72 (1H, m), 8.16 (1H, d, J=8Hz), 8.25 (1H, broad s)

(14) Phenyl 3-[2-(4-isobutylphenyl)-1-propenyl]benzoate
NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7Hz), 1.89 (1H, m), 2.30 (3H, d, J=1Hz), 2.50 (2H, d, J=7Hz), 6.87 (1H, d, J=1Hz), 7.1-7.6 (10H, m), 7.62 (1H, m), 8.08 (1H, m), 8.20 (1H, s)

(15) Phenyl 8-isobutyl-3,4,6,6-tetramethyl-6H-dibenzo-[b,d]pyrane-2-carboxylate
NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7Hz), 1.67 (6H, s), 1.89 (1H, m), 2.28 (3H, s), 2.50 (2H, d, J=7Hz), 2.61 (3H, s), 7.02 (1H, d, J=1Hz), 7.15 (1H, dd, J=1Hz, 8Hz), 7.2-7.5 (3H, m), 7.46 (2H, m), 7.72 (1H, d, J=8Hz), 8.41 (1H, s)

(16) Phenyl 3-[2,2-bis(4-isobutylphenyl)ethyl]benzoate
NMR ($CDCl_3$, δ) : 0.86 (12H, d, J=7Hz), 1.80 (2H, m), 2.40 (4H, d, J=7Hz), 3.41 (2H, d, J=7.5Hz), 4.17 (1H, t, J=7.5Hz), 7.02 (4H, d, J=8Hz), 7.12 (4H, d, J=8Hz), 7.0-7.3 (5H, m), 7.3-7.5 (2H, m), 7.88 (1H, br s), 7.95 (1H, d, J=7.5Hz)

(17) Phenyl 4-[2,2-bis(4-isobutylphenyl)ethyl]benzoate
mp : 97-98°C
NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=7Hz), 1.82 (2H, m),

2.41 (4H, d, J=7Hz), 3.41 (2H, d, J=7.5Hz), 4.18 (1H, t, J=7.5Hz), 7.3-7.0 (5H, m), 7.03 (4H, d, J=8Hz), 7.12 (4H, d, J=8Hz), 7.4-7.5 (2H, m), 8.00 (2H, d, J=9Hz)

(18) Phenyl 4-(4-isobutylphenoxy)benzoate
mp : 78°C
NMR ($CDCl_3$, δ) : 0.97 (6H, d, J=7Hz), 1.91 (1H, m), 2.53 (2H, d, J=7Hz), 7.04 (2H, d, J=8Hz), 7.06 (2H, d, J=8Hz), 7.2-7.4 (5H, m), 7.4-7.6 (2H, m), 8.18 (2H, d, J=8Hz)

(19) Benzyl phenyl 4,4'-biphenyldicarboxylate
Rf = 0.35 (CH_2-Cl_2:n-hexane (2:3))

(20) Phenyl 3-[N-(4-isobutylbenzyl)-N-(4-isobutylphenyl)-carbamoyl]benzoate
NMR ($CDCl_3$, δ) : 0.81 (6H, d, J=7Hz), 0.90 (6H, d, J=7Hz), 1.7-2.0 (2H, m), 2.37 (2H, d, J=7Hz), 2.47 (2H, d, J=7Hz), 5.12 (2H, s), 6.84 (2H, d, J=8Hz), 6.95 (2H, d, J=8Hz), 7.0-7.4 (8H, m), 7.4-7.5 (2H, m), 7.59 (1H, d, J=7.5Hz), 8.07 (1H, d, J=7.5Hz), 8.23 (1H, s)

(21) Phenyl 3-[N-(4-isobutylbenzoyl)-N-(4-isobutylphenyl)-aminomethyl]benzoate
NMR ($CDCl_3$, δ) : 0.7-0.9 (12H, m), 1.6-1.9 (2H, m), 2.3-2.5 (4H, m), 5.21 (2H, s), 6.7-7.0 (6H, m), 7.1-7.35 (5H, m), 7.35-7.6 (3H, m), 7.68 (1H, br s), 8.09 (2H, br s)

(22) Phenyl 3-[N-(4-isobutylbenzyl)-N-(4-isobutylphenyl)-aminomethyl]benzoate
NMR ($CDCl_3$, δ) : 0.8-0.9 (12H, m), 1.80 (2H, m), 2.3-2.5 (4H, m), 4.6-4.7 (4H, m), 6.69 (2H, br

s), 6.9-7.0 (2H, m), 7.0-7.3 (7H, m), 7.4-7.7 (4H, m), 8.07 (2H, br s)

(23) Phenyl 3-[N-(4-isobutylbenzoyl)-N-(3-isobutylphenyl)-aminomethyl]benzoate
NMR ($CDCl_3$, δ) : 0.65 (6H, d, J=7Hz), 0.81 (6H, d, J=7Hz), 1.52 (1H, m), 1.75 (1H, m), 2.25 (2H, d, J=7Hz), 2.35 (2H, d, J=7Hz), 5.22 (2H, s), 6.61 (1H, br s), 6.8-7.0 (4H, m), 7.0-7.3 (6H, m), 7.3-7.5 (3H, m), 7.68 (1H, d, J=7.5Hz), 8.0-8.2 (2H, m)

(24) Phenyl 3-[N-benzoyl-N-(4-isobutylphenyl)aminomethyl]-benzoate
NMR ($CDCl_3$, δ) : 0.78 (6H, d, J=7Hz), 1.74 (1H, m), 2.35 (2H, d, J=7Hz), 5.21 (2H, s), 6.83 (2H, d, J=8Hz), 6.92 (2H, d, J=8Hz), 7.1-7.6 (11H, m), 7.68 (1H, d, J=7.5Hz), 8.0-8.2 (2H, m)

(25) Phenyl 3-(4-isobutylphenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7Hz), 1.70-1.94 (1H, m), 2.42 (2H, d, J=8Hz), 5.12 (2H, s), 6.90 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.18-7.50 (5H, m), 7.53 (1H, t, J=8Hz), 7.74 (1H, dd, J=1Hz, 8Hz), 8.18 (1H, dd, J=1Hz, 8Hz), 8.28 (1H, t, J=1Hz)

(26) Phenyl 4-(4-propylphenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 0.92 (3H, t, J=7.5Hz), 1.50-1.70 (2H, m), 2.52 (2H, t, J=7.5Hz), 5.15 (2H, s), 6.90 (2H, d, J=8Hz), 7.10 (2H, d, J=8Hz), 7.20-7.50 (5H, m), 7.58 (2H, d, J=8Hz), 8.20 (2H, d, J=8Hz)

(27) Phenyl 2,3-dimethyl-5-(3-isobutylphenoxymethyl)-benzoate

NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7.5Hz), 1.80-2.00 (1H, m), 2.42 (3H, s), 2.48 (2H, d, J=7.5Hz), 2.58 (3H, s), 5.08 (2H, s), 6.78-6.90 (3H, m), 7.20-7.37 (4H, m), 7.45-7.52 (3H, m), 8.02 (1H, d, J=1Hz)

(28) Phenyl 2,3-dimethyl-5-(4-isobutylphenoxymethyl)-benzoate
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.70-1.92 (1H, m), 2.38 (3H, s), 2.42 (2H, d, J=7.5Hz), 2.55 (3H, s), 5.04 (2H, s), 6.90 (2H, d, J=8Hz), 7.07 (2H, d, J=8Hz), 7.18-7.32 (3H, m), 7.40-7.50 (3H, m), 7.95 (1H, d, J=1Hz)

(29) Phenyl 3-(2-isobutylphenoxymethyl)benzoate
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.85-2.12 (1H, m), 2.58 (2H, d, J=7.5Hz), 5.18 (2H, s), 6.83-6.98 (2H, m), 7.08-7.35 (5H, m), 7.35-7.63 (3H, m), 7.72 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.30 (1H, s)

(30) Phenyl 4-(4-isobutylphenyl)benzoate
NMR ($CDCl_3$, δ) : 0.95 (6H, d, J=7.5Hz), 1.80-2.04 (1H, m), 2.53 (2H, d, J=7.5Hz), 7.20-7.35 (5H, m), 7.42 (2H, d, J=8Hz), 7.59 (2H, d, J=8Hz), 7.72 (2H, d, J=8Hz), 8.25 (2H, d, J=8Hz)

(31) Phenyl 4'-isobutylstilbene-3-carboxylate
NMR ($CDCl_3$, δ) : 0.95 (6H, d, J=7.5Hz), 1.92 (1H, m), 2.52 (2H, d, J=7.5Hz), 7.10-7.40 (5H, m), 7.40-7.60 (5H, m), 7.78 (1H, m), 8.10 (1H, m), 8.38 (1H, m)

(32) Phenyl 4-[2-(4-isobutylphenyl)-1-propenyl]benzoate
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=0.75Hz), 1.90 (1H,

m), 2.30 (3H, d, J=0.4Hz), 2.50 (2H, d, J=7.5Hz), 6.90 (1H, s), 7.15-7.35 (5H, m), 7.40-7.55 (6H, m), 8.20 (2H, d, J=10Hz)

Preparation 52

A mixture of methyl 3-(chloroformyl)propionate (5.4 ml) and aluminum chloride (11.7 g) in dichloromethane was stirred at 25°C for 1 hour, and then a solution of 6-chloroindole (3.0 g) in dichloromethane (20 ml) at 25°C. The reaction mixture was stirred at 25°C for 1 hour, and poured into a mixture of ice and 1N hydrochloric acid. The organic layer was separated, washed with water, and dried over magnesium sulfate. After evaporation of the solvents the crystalline residue was recrystallized from ethyl acetate to give methyl 4-(6-chloroindol-3-yl)-4-oxobutyrate (2.54 g) as colorless crystals.

NMR ($CDCl_3$-CD_3OD, δ) : 2.80 (2H, t, J=7.5Hz), 3.19 (2H, t, J=7.5Hz), 3.70 (3H, s), 7.21 (1H, dd, J=2.5Hz, 8Hz), 7.39 (1H, d, J=2.5Hz), 7.85 (1H, s), 8.24 (1H, d, J=8Hz)

Preparation 53

1M solution of borane in tetrahydrofuran (4.6 ml) was added to a solution of methyl 4-(6-chloroindol-3-yl)-4-oxobutyrate (1.20 g) in tetrahydrofuran (40 ml) at 25°C over 5 minutes. The mixture was stirred at 25°C for 30 minutes, and 1M solution of borane in tetrahydrofuran 2.3 ml) was added at 25°C. The mixture was stirred at 25°C for 30 minutes, and then another 1M solution of borane in tetrahydrofuran (2.3 ml) was added at 25°C. The reaction mixture was stirred at 25°C for 15 minutes and poured into a mixture of ethyl acetate and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column

chromatography on silica gel (50 g) eluting with chloroform and by recrystallization from a mixture of ethyl acetate and hexane to give methyl 4-(6-chloroindol-3-yl)butyrate (669 mg) as pale yellow crystals.

NMR ($CDCl_3$, δ) : 1.92-2.15 (2H, m), 2.40 (2H, t, J=7.5Hz), 2.80 (2H, t, J=7.5Hz), 3.70 (3H, s), 7.00 (1H, d, J=2.5Hz), 7.10 (1H, dd, J=2.5Hz, 8Hz), 7.35 (1H, d, J=2.5Hz), 7.52 (1H, d, J=8Hz), 7.97 (1H, broad s)

Preparation 54

Methyl 4-(6-chloroindol-3-yl)butyrate (1.2 g) was hydrolyzed with 1N aqueous solution of sodium hydroxide (12 ml) and the crude product was recrystallized from a mixture of ethyl acetate and hexane to give 4-(6-chloroindol-3-yl)butyric acid (1.09 g) as colorless crystals.

NMR ($CDCl_3$-CD_3OD, δ) : 1.90-2.10 (2H, m), 2.38 (2H, t, J=7.5Hz), 2.79 (2H, t, J=7.5Hz), 6.98 (1H, s), 7.05 (1H, dd, J=2.5Hz, 8Hz), 7.35 (1H, d, J=2.5Hz), 7.50 (1H, d, J=8Hz)

Preparation 55

A solution of 3-indolebutyric acid (2.42 g) in N,N-dimethylformamide (20 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 1.05 g) in N,N-dimethylformamide (30 ml) at 25°C over 15 minutes. The mixture was stirred at 25°C for 1.5 hours and cooled to -40°C. A solution of phenyl 3-(methoxymethoxy)benzoate (3.07 g) in tetrahydrofuran (40 ml) was added at -40°C over 30 minutes, and the mixture was stirred at the same temperature for 30 minutes. The mixture was worked up in an usual manner, and the crude product was purified by column chromatography on silica gel (50 g) eluting with chloroform and recrystallization from a mixture of ethyl

acetate and hexane to give 4-[1-[3-(methoxymethoxy)-benzoyl]indol-3-yl]butyric acid (2.96 g) as colorless crystals.

NMR ($CDCl_3$, δ) : 2.03 (2H, tt, J=6Hz, 6Hz), 2.42 (2H, t, J=6Hz), 2.66 (2H, t, J=6Hz), 3.50 (3H, s), 5.36 (2H, s), 7.10 (1H, s), 7.2-7.6 (7H, m), 8.40 (1H, d, J=8Hz)

Preparation 56

The following compound was obtained according to a similar manner to that of Preparation 55.

4-[1-[4-(Methoxymethoxy)benzoyl]indol-3-yl]butyric acid

NMR ($CDCl_3$, δ) : 2.05 (2H, m), 2.45 (2H, t, J=8Hz), 2.75 (2H, t, J=8Hz), 3.52 (3H, s), 5.25 (2H, s), 6.7-7.4 (5H, m), 7.55 (1H, m), 7.70 (2H, d, J=8Hz), 8.45 (1H, m)

Preparation 57

A mixture of 4-[1-[4-(methoxymethoxy)benzoyl]-indol-3-yl]butyrate (2.50 g), benzyl bromide (1.81 g) and potassium carbonate (2.82 g) in N,N-dimethylformamide (30 ml) was stirred at 25°C for 6 hours. The mixture was diluted with ethyl acetate, washed with 1N hydrochloric acid, water, aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel (100 g) with dichloromethane to give benzyl 4-[1-[4-(methoxymethoxy)-benzoyl]indol-3-yl]butyrate (3.02 g) as a pale yellow oil.

NMR ($CDCl_3$, δ) : 2.05 (2H, m), 2.50 (2H, t, J=8Hz), 2.75 (2H, t, J=8Hz), 3.50 (3H, s), 5.10 (2H, s), 5.28 (2H, s), 7.1-7.2 (3H, m), 7.25-7.4 (7H, m), 7.55 (1H, m), 7.70 (2H, d, J=8Hz), 8.85 (1H, m)

Preparation 58

To a solution of 4-[1-[3-(methoxymethoxy)benzoyl]-indol-3-yl]butyric acid (1.4 g) in 1,4-dioxane (10 ml) was added 4N solution of hydrogen chloride in 1,4-dioxane (4 ml) at 25°C. The mixture was stirred at 25°C for 6 hours, and poured into a mixture of ether and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. After evaporation of the solvent, the crystalline residue was washed with isopropyl ether to give 4-[1-(3-hydroxybenzoyl)indol-3-yl]butyric acid (1.00 g) as colorless crystals.

NMR ($CDCl_3$-CD_3OD, δ) : 2.02 (2H, tt, J=6Hz, 6Hz), 2.40 (2H, t, J=6Hz), 2.75 (2H, t, J=6Hz), 7.05-7.2 (3H, m), 7.30-7.45 (4H, m), 7.6-7.7 (1H, m), 8.38 (1H, dd, J=2Hz, 8Hz)

Preparation 59

Benzyl 4-[1-[4-(methoxymethoxy)benzoyl]indol-3-yl]-butyrate (572 mg) was dissolved in trifluoroacetic acid (12 ml) at 25°C and the mixture was stirred at the same temperature for 15 minutes. After evaporation of the solvent, the residue was dissolved with ethyl acetate, washed with aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel (30 g) eluting with a mixture of hexane and ethyl acetate (2:1) to give benzyl 4-[1-(4-hydroxybenzoyl)indol-3-yl]butyrate (350 mg) as a yellow oil.

NMR ($CDCl_3$, δ) : 2.10 (2H, m), 2.50 (2H, t, J=8Hz), 2.80 (2H, t, J=8Hz), 5.15 (2H, s), 6.98 (2H, d, J=10Hz), 7.2-7.6 (7H, m), 7.60 (1H, m), 7.65 (2H, d, J=10Hz), 8.40 (1H, m)

Example 1

A solution of 4-(indol-3-yl)butyric acid (1.25 g) in N,N-dimethylformamide (10 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 541 mg) in N,N-dimethylformamide (20 ml) at 25°C over 15 minutes. The mixture was stirred at 25°C for 1 hour, and then a solution of phenyl 3-(3-isobutylphenoxymethyl)benzoate (2.22 g) in tetrahydrofuran (10 ml) was added at -40°C. The reaction mixture was stirred at -40°C for 30 minutes and poured into a mixture of ether and 1N hydrochloric acid. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. The residue was purified by column chromatography on silica gel (40 g) eluting with chloroform and by recrystallization from a mixture of ethyl acetate and hexane to give 4-[1-[3-(3-isobutylphenoxymethyl)benzoyl]indol-3-yl]butyric acid (1.45 g) as colorless crystals.

mp : 81-83°C

NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=4Hz), 1.88 (1H, m), 2.06 (2H, quintet, J=4Hz), 2.45 (2H, t, J=4Hz), 2.47 (2H, d, J=4Hz), 2.76 (2H, t, J=4Hz), 5.16 (2H, s), 6.75-6.87 (3H, m), 7.09 (1H, s), 7.20-7.77 (7H, m), 7.83 (1H, s), 8.40 (1H, dd, J=1Hz, 4Hz)

Example 2

The following compounds were obtained according to a similar manner to that of Example 1.

(1) 4-[1-[3-(4-Isopentylphenoxymethyl)benzoyl]indol-3-yl]butyric acid

mp : 114-116°C

NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=4Hz), 1.4-1.7 (3H, m), 2.01 (2H, m), 2.42 (2H, t, J=4Hz), 2.54 (2H, dd, J=4Hz, 5Hz), 2.72 (2H, t, J=4Hz), 5.10 (2H,

s), 6.90 (2H, d, J=5Hz), 7.05-7.70 (9H, m), 7.80 (1H, t, J=1Hz), 8.38 (1H, dd, J=1Hz, 5Hz)

(2) 4-[1-[4-(4-Isobutylbenzyloxy)benzoyl]indol-3-yl]-butyric acid
mp : 156°C
NMR ($CDCl_3$, δ) : 0.95 (6H, d, J=7.5Hz), 1.8-2.2 (3H, m), 2.4-2.6 (4H, m), 2.78 (2H, t, J=7.5Hz), 5.15 (2H, s), 7.12 (2H, d, J=10Hz), 7.2-7.5 (7H, m), 7.60 (1H, m), 7.75 (2H, d, J=10Hz), 8.35 (1H, m)

(3) 4-[1-[3-[Bis(4-isobutylbenzyl)amino]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.92 (12H, d, J=7.5Hz), 1.65-2.0 (2H, m), 2.0-2.1 (2H, m), 2.42 (2H, t, J=7.5Hz), 2.48 (4H, d, J=7.5Hz), 2.70 (2H, t, J=7.5Hz), 4.70 (4H, s), 6.9-7.1 (2H, m), 7.1-7.2 (8H, m), 7.25-7.5 (5H, m), 7.5-7.6 (1H, m), 8.40 (1H, d, J=7.5Hz)

(4) 4-[1-[2,3-Dimethyl-4-[1-(4-isobutylphenyl)ethoxy]-benzoyl]indol-3-yl]butyric acid
mp : 98-99°C
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7Hz), 1.67 (3H, d, J=6Hz), 1.85 (1H, m), 1.97 (2H, m), 2.22 (3H, s), 2.31 (3H, s), 2.3-2.5 (5H, m), 2.69 (2H, t, J=7.5Hz), 5.36 (1H, q, J=6Hz), 6.66 (1H, d, J=9Hz), 6.86 (1H, s), 7.04 (1H, d, J=9Hz), 7.11 (2H, d, J=8Hz), 7.2-7.4 (4H, m), 7.5-7.6 (1H, m), 8.23 (1H, d, J=7.5Hz)

(5) 4-[1-[3-[1-(4-Isobutylphenyl)ethoxy]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.87 (6H, d, J=4Hz), 1.64 (3H, d, J=4Hz), 1.80 (1H, m), 1.98 (2H, quintet, J=4Hz),

2.40 (2H, t, J=4Hz), 2.41 (2H, d, J=4Hz), 2.72 (2H, t, J=4Hz), 5.32 (1H, q, J=4Hz), 6.8-7.4 (11H, m), 7.53 (1H, dd, J=2Hz, 5Hz), 8.35 (1H, dd, J=2Hz, 5Hz)

(6) 4-[1-[4,5-Dimethyl-3-[1-(4-isobutylphenyl)ethoxy]-benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.62 (3H, d, J=7.5Hz), 1.68-2.08 (3H, m), 2.22-2.49 (10H, m), 2.58-2.80 (2H, m), 6.78-6.88 (1H, m), 6.92-7.02 (2H, m), 7.02-7.16 (3H, m), 7.20-7.40 (3H, m), 7.48-7.60 (1H, m), 8.28-8.38 (1H, m)

(7) 4-[1-[3-(3,4-Dichlorophenoxymethyl)benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 1.90-2.10 (2H, m), 2.40 (2H, t, J=7.5Hz), 2.73 (2H, t, J=7.5Hz), 5.14 (2H, s), 6.84 (1H, dd, J=2.5Hz, 10Hz), 7.05 (1H, s), 7.09 (1H, d, J=2.5Hz), 7.20-7.45 (3H, m), 7.50-7.75 (4H, m), 7.78 (1H, s), 8.38 (1H, d, J=8Hz)

(8) 4-[1-[3-[Bis(4-isobutylphenyl)methylthio]benzoyl]-indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.85 (12H, d, J=6Hz), 1.80 (2H, m), 2.02 (2H, m), 2.36-2.50 (4H, m), 2.72 (2H, t, J=6Hz), 5.55 (1H, s), 6.95 (1H, s), 7.05 (4H, d, J=8Hz), 7.2-7.5 (9H, m), 7.5-7.6 (2H, m), 8.26 (1H, d, J=8Hz)

(9) 4-[5-Chloro-1-[3-(3-isobutylphenoxymethyl)benzoyl]-indol-3-yl]butyric acid
mp : 96-97°C
NMR ($CDCl_3$, δ) : 0.88 (6H, d, J=7.5Hz), 1.70-2.10 (3H, m), 2.30-2.50 (4H, m), 2.69 (2H, t, J=7.5Hz), 5.10 (2H, s), 6.70-6.85 (3H, m), 7.10

(1H, s), 7.20 (1H, t, J=8Hz), 7.32 (1H, dd, J=2.5Hz, 8Hz), 7.45-7.75 (4H, m), 7.80 (1H, s), 8.30 (1H, d, J=8Hz)

(10) 4-[6-Chloro-1-[3-(3-isobutylphenoxymethyl)benzoyl]-indol-3-yl]butyric acid
mp : 126-127°C
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7.5Hz), 1.72-2.10 (3H, m), 2.35-2.50 (4H, m), 2.70 (2H, t, J=9.5Hz), 5.5 (2H, s), 6.70-6.85 (3H, m), 7.05 (1H, s), 7.12-7.38 (2H, m), 7.40-7.75 (4H, m), 7.80 (1H, s), 8.49 (1H, d, J=2.5Hz)

(11) 4-[1-[3-(3,4-Dichlorobenzyloxy)benzoyl]indol-3-yl]-butyric acid
NMR ($CDCl_3$, δ) : 1.90-2.15 (2H, m), 2.41 (2H, t, J=7.5Hz), 2.71 (2H, t, J=7.5Hz), 5.02 (2H, s), 7.02 (1H, s), 7.12-7.65 (10H, m), 8.35 (1H, d, J=8Hz)

(12) 4-[1-[3-(3-Bromophenoxymethyl)benzoyl]indol-3-yl]-butyric acid
NMR ($CDCl_3$, δ) : 1.85-2.15 (2H, m), 2.42 (2H, t, J=7.5Hz), 2.70 (2H, t, J=7.5Hz), 5.10 (2H, s), 6.83-6.95 (1H, m), 7.00-7.20 (4H, m), 7.20-7.50 (2H, m), 7.50-7.75 (4H, m), 7.80 (1H, broad s), 8.38 (1H, d, J=8Hz)

(13) 4-[1-[3-[3-(Isopropoxy)phenoxymethyl]benzoyl]-indol-3-yl]butyric acid
mp : 80-82°C
NMR ($CDCl_3$, δ) : 1.33 (6H, d, J=7.5Hz), 1.90-2.13 (2H, m), 2.42 (2H, t, J=7.5Hz), 2.75 (2H, t, J=7.5Hz), 4.40-4.62 (1H, m), 5.11 (2H, s), 6.45-6.60 (3H, m), 7.08 (1H, s), 7.10-7.25 (1H,

m), 7.28-7.48 (2H, m), 7.48-7.63 (2H, m), 7.63-7.74 (2H, m), 7.81 (1H, broad s), 8.38 (1H, m)

(14) 4-[1-[3-[2-(4-Isobutylphenyl)-1-propenyl]benzoyl]-indol-3-yl]butyric acid
mp : 109-110°C
NMR ($CDCl_3$, δ) : 0.92 (6H, 7H), 1.87 (1H, m), 2.02 (2H, m), 2.30 (3H, d, J=1Hz), 2.4-2.6 (4H, m), 2.76 (2H, t, J=7.5Hz), 6.87 (1H, d, J=1Hz), 7.1-7.2 (3H, m), 7.3-7.6 (8H, m), 7.70 (1H, s), 8.40 (1H, m)

(15) 4-[1-[8-Isobutyl-3,4,6,6-tetramethyl-6H-dibenzo[b,d]-pyran-2-ylcarbonyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.95 (3H, d, J=7Hz), 1.70 (6H, s), 1.90 (1H, m), 2.03 (2H, m), 2.44 (2H, t, J=7.5Hz), 2.52 (2H, d, J=7Hz), 2.74 (2H, t, J=7.5Hz), 7.0-7.2 (3H, m), 7.2-7.5 (2H, m), 7.5-7.7 (3H, m), 8.33 (1H, m)

(16) 4-[1-[3-[2,2-Bis(4-isobutylphenyl)ethyl]benzoyl]-indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.80 (12H, d, J=7Hz), 1.75 (2H, m), 2.01 (2H, m), 2.3-2.5 (2H, m), 2.36 (4H, d, J=7Hz), 2.73 (2H, t, J=7.5Hz), 3.39 (2H, d, J=7.5Hz), 4.16 (1H, t, J=7.5Hz), 7.0-7.4 (6H, m), 7.00 (4H, d, J=8Hz), 7.10 (4H, d, J=8Hz), 7.4-7.5 (1H, m), 7.55 (1H, m), 8.25 (1H, m)

(17) 4-[1-[4-[2,2-Bis(4-isobutylphenyl)ethyl]benzoyl]-indol-3-yl]butyric acid
mp : 152°C
NMR ($CDCl_3$, δ) : 0.87 (12H, d, J=7Hz), 1.82 (2H, m),

1.9-2.1 (2H, m), 2.3-2.5 (2H, m), 2.42 (4H, d, J=7Hz), 2.74 (2H, t, J=7.5Hz), 3.42 (2H, d, J=7.5Hz), 4.20 (1H, t, J=7.5Hz), 7.0-7.2 (1H, m), 7.03 (4H, d, J=8Hz), 7.12 (4H, d, J=8Hz), 7.2-7.4 (2H, m), 7.5-7.6 (1H, m), 7.10 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 8.28 (1H, m)

(18) 4-[1-[4-(4-Isobutylphenoxy)benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.93 (6H, d, J=7Hz), 1.87 (1H, m), 2.04 (2H, quint, J=7.5Hz), 2.4-2.6 (4H, m), 2.76 (2H, t, J=7.5Hz), 7.01 (2H, d, J=8Hz), 7.05 (2H, d, J=8Hz), 7.16 (1H, s), 7.18 (2H, d, J=8Hz), 7.2-7.5 (2H, m), 7.57 (1H, d, J=7.5Hz), 7.71 (2H, d, J=8Hz), 8.35 (1H, d, J=7.5Hz)

(19) 4-[1-[4-(4'-Benzyloxycarbonyl)biphenylcarbonyl]-indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 2.03 (2H, m), 2.43 (2H, t, J=7.5Hz), 2.75 (2H, t, J=7.5Hz), 5.41 (2H, s), 7.13 (1H, s), 7.2-7.5 (7H, m), 7.58 (1H, d, J=7.5Hz), 7.72 (2H, d, J=8Hz), 7.76 (2H, d, J=8Hz), 7.83 (2H, d, J=8Hz), 8.18 (2H, d, J=8Hz), 8.41 (1H, d, J=7.5Hz)

(20) 4-[1-[3-[N-(4-Isobutylbenzoyl)-N-methylamino]-benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.81 (6H, d, J=6Hz), 1.7-1.9 (1H, m), 2.00 (2H, t, J=7Hz), 2.3-2.5 (4H, m), 2.71 (2H, t, J=7Hz), 3.52 (3H, s), 6.8-7.1 (4H, m), 7.2-7.6 (8H, m), 8.29 (1H, m)

(21) 4-[1-[3-[N-(4-Isobutylbenzyl)-N-(4-isobutylphenyl)-carbamoyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.78 (6H, d, J=7Hz), 0.86 (6H, d,

J=7Hz), 1.6-1.9 (2H, m), 2.06 (2H, quint, J=7Hz), 2.3-2.5 (6H, m), 2.80 (2H, t, J=7Hz), 5.08 (2H, s), 6.76 (2H, d, J=8Hz), 6.91 (2H, d, J=8Hz), 6.94 (1H, s), 7.04 (2H, d, J=8Hz), 7.16 (2H, d, J=8Hz), 7.1-7.5 (4H, m), 7.5-7.7 (2H, m), 7.84 (1H, br s), 8.37 (1H, d, J=7.5Hz)

(22) 4-[1-[3-[N-(4-Isobutylbenzoyl)-N-(4-isobutylphenyl)-aminomethyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.80 (12H, d, J=7Hz), 1.75 (2H, m), 2.05 (2H, quint, J=7Hz), 2.38 (4H, d, J=7Hz), 2.43 (2H, t, J=7.5Hz), 2.77 (2H, t, J=7Hz), 5.23 (2H, s), 6.83 (2H, d, J=8Hz), 6.90 (2H, d, J=8Hz), 6.94 (2H, d, J=8Hz), 7.11 (1H, s), 7.20 (2H, d, J=8Hz), 7.3-7.5 (4H, m), 7.59 (1H, d, J=7.5Hz), 7.6-7.8 (1H, m), 7.77 (1H, br s), 8.45 (1H, d, J=7.5Hz)

(23) 4-[1-[3-[N-(4-Isobutylbenzoyl)-(3-isobutylphenyl)-aminomethyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.64 (6H, d, J=7Hz), 0.80 (6H, d, J=7Hz), 1.51 (1H, m), 1.74 (1H, m), 2.25 (2H, d, J=7Hz), 2.33 (2H, d, J=7Hz), 2.42 (2H, t, J=7Hz), 2.74 (2H, t, J=7Hz), 5.21 (2H, s), 6.59 (1H, br s), 6.8-7.0 (4H, m), 7.0-7.3 (4H, m), 7.5-7.3 (4H, m), 7.57 (1H, d, J=7.5Hz), 7.6-7.8 (1H, m), 7.75 (1H, br s), 8.42 (1H, d, J=7.5Hz)

(24) 4-[1-[3-[N-(4-Isobutylbenzyl)-N-(4-isobutylphenyl)-aminomethyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.86 (6H, d, J=7Hz), 0.88 (6H, d, J=7Hz), 1.78 (2H, m), 1.98 (2H, quint, J=7.5Hz), 2.3-2.5 (6H, m), 2.70 (2H, t, J=7.5Hz), 4.6-4.7 (4H, m), 6.70 (1H, br s), 6.8-7.7 (15H, m), 8.35 (1H, d, J=7.5Hz)

(25) 4-[1-[3-[N-Benzoyl-N-(4-isobutylphenyl)aminomethyl]-benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.78 (6H, d, J=7Hz), 1.74 (1H, m), 2.35 (2H, d, J=7Hz), 5.21 (2H, s), 6.83 (2H, d, J=8Hz), 6.92 (2H, d, J=8Hz), 7.1-7.6 (11H, m), 7.68 (1H, d, J=7.5Hz), 8.0-8.2 (2H, m)

(26) 4-[1-[3-(4-Isobutylphenoxymethyl)benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7Hz), 1.70-1.92 (1H, m), 1.95-2.12 (2H, m), 2.36-2.50 (4H, m), 2.75 (2H, t), 5.12 (2H, s), 6.88 (2H, d, J=8Hz), 7.07 (2H, d, J=8Hz), 7.08 (1H, s), 7.20-7.72 (6H, m), 7.80 (1H, s), 8.38 (1H, dd, J=1Hz, 8Hz)

(27) 4-[1-[4-(4-Propylbenzyloxy)benzoyl]indol-3-yl]-butyric acid
mp : 93-94°C
NMR ($CDCl_3$, δ) : 0.92 (3H, t, J=7.5Hz), 1.52-1.72 (2H, m), 1.95-2.22 (2H, m), 2.43 (2H, t, J=7.5Hz), 2.55 (2H, t, J=7.5Hz), 2.76 (2H, t, J=7.5Hz), 5.15 (2H, s), 6.92 (2H, d, J=8Hz), 7.08 (1H, s), 7.12 (2H, d, J=8Hz), 7.30-7.62 (5H, m), 7.75 (2H, d, J=8Hz), 8.38 (1H, dd, J=1Hz, 8Hz)

(28) 4-[1-[2,3-Dimethyl-5-(3-isobutylphenoxymethyl]-benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.75-2.10 (3H, m), 2.23 (3H, s), 2.38 (3H, s), 2.43-2.52 (4H, m), 2.72 (2H, t, J=7.5Hz), 5.07 (2H, s), 6.75-6.90 (4H, m), 7.20 (1H, dd, J=6Hz, 8Hz), 7.30-7.50 (5H, m), 7.58 (1H, dd, J=1Hz, 8Hz)

(29) 4-[1-[2,3-Dimethyl-5-(4-isobutylphenoxymethyl)-

benzoyl]indol-3-yl]butyric acid
NRM ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.7-2.1 (3H, m), 2.24 (3H, s), 2.40 (3H, s), 2.41-2.48 (4H, m), 2.72 (2H, t, J=7.5Hz), 5.06 (2H, s), 6.84 (1H, broad s), 6.90 (2H, d, J=8Hz), 7.08 (2H, d, J=8Hz), 7.28-7.46 (5H, m), 7.48 (1H, dd, J=1Hz, 8Hz)

(30) 4-[1-[3-(2-Isobutylphenoxymethyl)benzoyl]indol-3-yl]-butyric acid
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7.5Hz), 1.81-2.15 (3H, m), 2.44 (2H, t, J=7.5Hz), 2.58 (2H, d, J=7.5Hz), 2.75 (2H, t, J=7.5Hz), 5.18 (2H, s), 6.83-7.02 (2H, m), 7.02-7.25 (3H, m), 7.25-7.50 (2H, m), 7.50-7.90 (5H, m), 8.40 (1H, m)

(31) 4-[1-[4-(4-Isobutylphenyl)benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.92 (6H, d, J=7.5Hz), 1.78-2.14 (4H, m), 2.42 (2H, t, J=7.5Hz), 2.54 (2H, d, J=7.5Hz), 2.76 (2H, t, J=7.5Hz) 7.17 (1H, s), 7.20-7.45 (4H, m), 7.58 (3H, d, J=8Hz), 7.77 (4H, A_2B_2, J=8Hz), 8.40 (1H, d, J=8Hz)

(32) 4-[1-[3-[2-(4-Isobutylphenyl)vinyl]benzoyl]indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.90 (6H, d; J=7.5Hz), 1.88 (1H, m), 2.01 (2H, m), 2.35-2.50 (4H, m), 2.75 (2H, t, J=7.5Hz), 7.0-7.6 (12H, m), 7.77 (1H, m), 7.87 (1H, m), 8.40 (1H, m)

(33) 4-[1-[4-[2-(4-Isobutylphenyl)-1-propenyl]benzoyl]-indol-3-yl]butyric acid
NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=0.75Hz), 1.90 (1H, m), 2.02 (2H, m), 2.35 (3H, t, J=0.5Hz),

2.45-2.55 (4H, m), 2.75 (2H, t, J=5Hz), 6.88 (1H, s), 7.12-7.20 (3H, m), 7.30-7.60 (7H, m), 7.75 (2H, d, J=7.5Hz), 8.40 (1H, m)

Example 3

A solution of 4-[1-(3-hydroxybenzoyl)indol-3-yl]-butyric acid (480 mg) in N,N-dimethylformamide (10 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 131 mg) in N,N-dimethylformamide at 25°C over 15 minutes. The mixture was stirred at 25°C for 30 minutes, and then a solution of bis(4-isobutylphenyl)-bromomethane (640 mg) in tetrahydrofuran (10 ml) was added at 25°C. The reaction mixture was stirred at 25°C for 4 hours and allowed to stand at 25°C for 2 days. The mixture was worked up in an usual manner and the crude product was purified by column chromatography on silica gel (40 g) eluting with chloroform to give 4-[1-[3-[bis-(4-isobutylphenyl)methoxy]benzoyl]indol-3-yl]butyric acid (0.37 g) as a colorless oil.

NMR ($CDCl_3$, δ) : 0.88 (12H, d, J=6Hz), 1.86 (2H, m), 2.02 (2H, m), 2.37-2.50 (4H, m), 2.62 (2H, t, J=6Hz), 6.23 (1H, s), 7.00 (1H, s), 7.10 (4H, d, J=8Hz), 7.15-7.40 (10H, m), 7.58 (1H, m), 8.47 (1H, dd, J=2Hz, 8Hz)

Example 4

The following compounds were obtained according to a similar manner to that of Example 3.

(1) Benzyl 4-[1-[4-[bis(4-isobutylphenyl)methoxy]-benzoyl]indol-3-yl]butyrate

NMR ($CDCl_3$, δ) : 0.90 (12H, d, J=5Hz), 1.85 (2H, m), 2.05 (2H, m), 2.35-2.80 (6H, m), 2.70 (2H, t, J=8Hz), 5.10 (2H, s), 6.28 (1H, s), 7.00-7.40 (18H, m), 7.50 (1H, m), 7.65 (1H, m), 8.30 (1H, m)

(2) Benzyl 4-[1-[4-[1-(4-isobutylphenyl)ethoxy]benzoyl]-indol-3-yl]butyrate

NMR ($CDCl_3$, δ) : 0.85 (6H, d, J=5Hz), 1.62 (3H, d, J=7Hz), 1.80 (1H, m), 2.00 (2H, m), 2.8-2.95 (4H, m), 2.65 (2H, t, J=8Hz), 5.02 (2H, s), 5.32 (1H, q, J=7Hz), 6.90 (2H, d, J=10Hz), 7.00-7.10 (3H, m), 7.15-7.45 (9H, m), 7.42 (1H, m), 7.55 (2H, d, J=10Hz), 8.23 (1H, m)

Example 5

A mixture of benzyl 4-[1-[4-[bis(4-isobutylphenyl)-methoxy]benzoyl]indol-3-yl]butyrate (500 mg) and 10% palladium on activated carbon (50 mg) in 1,4-dioxane (10 ml) was stirred under hydrogen atmosphere (1 atm) at 25°C for 8 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was treated with isopropyl ether and the solid was filtered to give 4-[1-[4-[bis(4-isobutylphenyl)methoxy]benzoyl]indol-3-yl]butyric acid (162 mg) as white powder.

NMR ($CDCl_3$, δ) : 0.90 (12H, d, J=5Hz), 1.80 (2H, m), 2.05 (2H, m), 2.35-2.50 (6H, m), 2.72 (2H, t, J=8Hz), 6.25 (1H, s), 7.00-7.20 (7H, m), 7.25-7.40 (6H, m), 7.55 (1H, m), 7.65 (2H, d, J=10Hz), 8.30 (1H, m)

Example 6

The following compound was obtained according to a similar manner to that of Example 5.

4-[1-[4-[1-(4-Isobutylphenyl)ethoxy]benzoyl]-indol-3-yl]butyric acid

NMR ($CDCl_3$, δ) : 0.85 (6H, d, J=6Hz), 1.65 (3H, d, J=7Hz), 1.85 (1H, m), 2.00 (2H, m), 2.35-2.50 (4H, m), 2.72 (2H, t, J=8Hz), 5.40 (1H, q, J=7Hz), 6.95 (2H, d, J=10Hz), 7.05-7.20 (3H, m),

7.20-7.40 (4H, m), 7.50-7.70 (3H, m), 8.30 (1H, m)

Example 7

4N-Hydrogen chloride in 1,4-dioxane (1 ml) was added to a solution of methoxymethyl 4-[1-[4-(4'-tert-butylcarbamoyl)biphenylcarbonyl]indol-3-yl]butyrate (30 mg) in 1,4-dioxane (0.5 ml). The mixture was stirred at room temperature for 20 minutes and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was washed with diisopropyl ether to give 4-[1-[4-(4'-tert-butylcarbamoyl)biphenylcarbonyl]indol-3-yl]butyric acid as a white powder (12.1 mg).

mp : 174-175°C

NMR ($CDCl_3$, δ) : 1.51 (9H, s), 2.03 (2H, m), 2.44 (2H, t, J=7.5Hz), 2.76 (2H, t, J=7.5Hz), 6.04 (1H, br s), 7.14 (1H, s), 7.3-7.5 (2H, m), 7.59 (1H, d, J=7.5Hz), 7.6-7.9 (8H, m), 8.41 (1H, d, J=7.5Hz)

Example 8

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30 mg) and 1-hydroxybenzotriazole (20 mg) was added to a mixture of methoxymethyl 4-[1-[4-(4'-carboxy)biphenylcarbonyl]indol-3-yl]butyrate (40 mg) and tert-butylamine (15 mg) in dichloromethane (3 ml). The mixture was stirred at room temperature for 5 hours and poured into ice water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by thin-layer chromatography on silica gel using a mixture of n-hexane and ethyl acetate (1:1) as the eluent. Appropriate fractions were combined, extracted with ethyl acetate and evaporated to give methoxymethyl 4-[1-[4-[4'-tert-butylcarbamoyl)biphenyl-

carbonyl]indol-3-yl]butyrate (26 mg) as a colorless foam.

NMR ($CDCl_3$, δ) : 1.52 (9H, s), 2.05 (2H, m), 2.45 (2H, t, J=7.5Hz), 2.76 (2H, t, J=7.5Hz), 3.44 (3H, s), 5.21 (2H, s), 6.02 (1H, br s), 7.15 (1H, s), 7.3-7.5 (2H, m), 7.61 (1H, d, J=7.5Hz), 7.3-7.4 (8H, m), 8.42 (1H, d, J=7.5Hz)

Example 9

A mixture of methoxymethyl 4-[1-[4-(4'-benzyloxycarbonyl)biphenylcarbonyl]indol-3-yl]butyrate (0.70 g) and 10% palladium on carbon (0.26 g) in ethyl acetate (30 ml) was shaken under hydrogen atmosphere (3.5 atm) at room temperature for 2 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was washed with diisopropyl ether to give methoxymethyl 4-[1-[4-(4'-carboxy)biphenylcarbonyl]indol-3-yl]butyrate (0.21 g) as a white powder.

mp : 188-189°C

NMR ($CDCl_3$, δ) : 2.06 (2H, m), 2.46 (2H, t, J=7.5Hz), 2.77 (2H, t, J=7.5Hz), 3.43 (3H, s), 5.22 (2H, s), 7.14 (1H, s), 7.3-7.5 (2H, m), 7.61 (1H, d, J=7.5Hz), 7.7-8.0 (6H, m), 8.26 (2H, d, J=8Hz), 8.42 (1H, d, J=7.5Hz)

Example 10

Chloromethyl methyl ether (0.17 ml) was added to a mixture of 4-[1-[4-(4'-benzyloxycarbonyl)biphenylcarbonyl]indol-3-yl]butyric acid (0.55 g) and potassium carbonate (0.21 g) in dimethylformamide (10 ml). The mixture was stirred at room temperature for 5 hours and partitioned between ethyl acetate and water. The organic layer was washed with water, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (40 g) using a mixture of n-hexane and ethyl acetate (5:1) as an eluent.

Appropriate fractions were combined and evaporated to give methoxymethyl 4-[1-[4-(4'-benzyloxycarbonyl)biphenylcarbonyl]indol-3-yl]butyrate (0.51 g) as a colorless foam.

NMR ($CDCl_3$, δ) : 2.05 (2H, m), 2.45 (2H, t, J=7.5Hz), 2.76 (2H, t, J=7.5Hz), 3.44 (3H, s), 5.21 (2H, s), 5.41 (2H, s), 7.14 (1H, s), 7.3-7.6 (7H, m), 7.61 (1H, d, J=7.5Hz), 7.74 (2H, d, J=8Hz), 7.78 (2H, d, J=8Hz), 7.84 (2H, d, J=8Hz), 8.21 (2H, d, J=8Hz), 8.41 (1H, d, J=7.5Hz)

Example 11

A mixture of 4-[1-[4-[2-(4-isobutylphenyl)-1-propenyl]benzoyl]indol-3-yl]butyric acid (200 mg) and 10% palladium on activated carbon (60 mg) in 1,4-dioxane (10 ml) was shaken under hydrogen atmosphere (2 atm) at 25°C for 3 hours. The catalyst was filtered off, and the filtrate was evaporated. The crystalline residue was washed with isopropyl ether to give 4-[1-[4-[2-(4-isobutylphenyl)propyl]benzoyl]indol-3-yl]butyric acid (151 mg) as yellow crystals.

NMR ($CDCl_3$, δ) : 0.90 (6H, d, J=7.5Hz), 1.30 (3H, d, J=5Hz), 1.85 (1H, m), 2.00 (2H, m), 2.40 (4H, m), 2.75 (2H, t, J=5Hz), 2.85-3.10 (3H, m), 7.00-7.10 (5H, m), 7.18 (2H, d, J=6Hz), 7.25-7.40 (2H, m), 7.55-7.65 (3H, m), 8.32 (1H, m)

Example 12

The following compounds were obtained according to a similar manner to that of Example 11.

(1) 4-[1-[3-[2-(4-Isobutylphenyl)propyl]benzoyl]-indol-3-yl]butyric acid

mp : 77-78°C

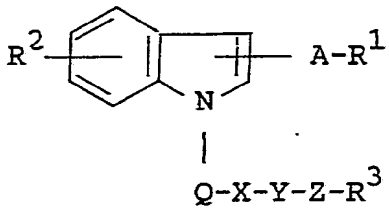
NMR ($CDCl_3$, δ) : 0.85 (6H, d, J=7Hz), 1.27 (3H, d, J=6Hz), 1.79 (1H, m), 2.03 (2H, m), 2.41 (2H, d, J=7Hz), 2.43 (2H, t, J=7.5Hz), 2.75 (2H, t, J=7.5Hz), 2.7-3.1 (3H, m), 7.0-7.1 (5H), 7.2-7.6 (7H, m), 8.31 (1H, m)

(2) 4-[1-[3-(4-Isobutylphenethyl)benzoyl]indol-3-yl]-butyric acid

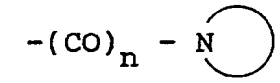
NMR ($CDCl_3$, δ) : 0.89 (6H, d, J=7.5Hz), 1.80 (1H, m), 2.00 (2H, m), 2.35-2.50 (4H, m), 2.74 (2H, t, J=7.5Hz), 2.80-3.10 (4H, m), 7.00-7.15 (5H, m), 7.30-7.45 (4H, m), 7.45-7.60 (3H, m), 8.35 (1H, m)

CLAIMS

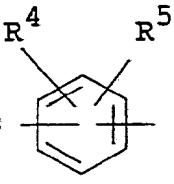
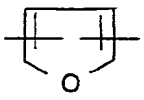
1. A compound of the formula :



wherein R^1 is carboxy or protected carboxy,
R^2 is hydrogen, lower alkyl or halogen,
R^3 is aryl or ar(lower)alkyl, each of which may have suitable substituent(s), or a group of the formula :



in which  is heterocyclic group containing nitrogen atom, and
n is 0 or 1,
A is lower alkylene which may be substituted by oxo or lower alkenylene,
Q is carbonyl, sulfonyl or lower alkylene,

X is  or 

in which R^4 is hydrogen or lower alkyl, and
R^5 is hydrogen, lower alkyl or $Y\text{-}Z\text{-}R^3$,

Y is bond or lower alkylene,

Z is bond, lower alkylene, lower alkenylene,

$$-O-,\ -S-\ \text{or}\ -\overset{R^6}{\underset{|}{N}}-,$$

in which R^6 is lower alkyl, ar(lower)alkyl which may have suitable substituent(s) or amino protective group; or

$X-Y-Z-R^3$ is 6H-dibenzo[b,d]pyranyl which may have suitable substituent(s),

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein

R^1 is carboxy or esterified carboxy,

R^3 is aryl which may be substituted by one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and lower alkylcarbamoyl, ar(lower)alkyl which may be substituted by one to three substituent(s) selected from lower alkyl, halogen, cyano, carboxy, esterified carboxy, amidated carboxy and oxo, and

R^6 is lower alkyl, ar(lower)alkyl which may be substituted by lower alkyl.

3. A compound of claim 2, wherein

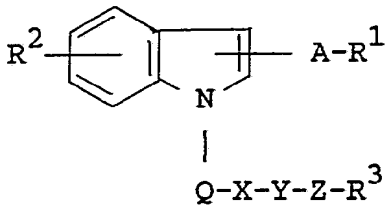
R^1 is carboxy, lower alkoxycarbonyl or mono- or di- or triphenyl(lower)alkoxycarbonyl,

R^3 is phenyl substituted by one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, halogen and lower alkylcarbamoyl, mono- or di- or triphenyl(lower)alkyl which may be substituted by one to three substituents

selected from lower alkyl, halogen, cyano, carboxy, mono- or di- or tri phenyl(lower)alkoxycarbonyl, mono- or di(lower)alkylcarbamoyl, phenylcarbamoyl, lower alkylphenylcarbamoyl and oxo

R^6 is lower alkyl, mono- or di- or triphenyl(lower)-alkyl which may be substituted by lower alkyl.

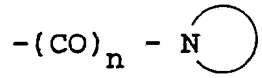
4. A process for preparing a compound of the formula :



wherein R^1 is carboxy or protected carboxy,

R^2 is hydrogen, lower alkyl or halogen,

R^3 is aryl or ar(lower)alkyl, each of which may have suitable substituent(s), or a group of the formula :

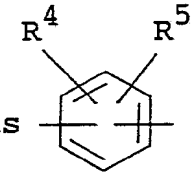
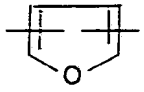


in which  is heterocyclic group containing nitrogen atom, and

n is 0 or 1,

A is lower alkylene which may be substituted by oxo or lower alkenylene,

Q is carbonyl, sulfonyl or lower alkylene,

X is  or 

in which R^4 is hydrogen or lower alkyl, and

R^5 is hydrogen, lower alkyl or $Y-Z-R^3$,

Y is bond or lower alkylene,

Z is bond, lower alkylene, lower alkenylene, $-O-$, $-S-$ or $-\overset{R^6}{\underset{|}{N}}-$,

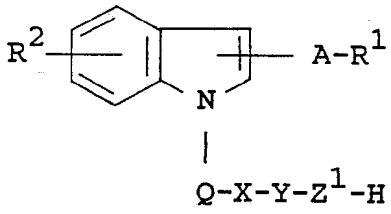
in which R^6 is lower alkyl, ar(lower)alkyl which may have suitable substituent(s) or amino protective group; or

$X-Y-Z-R^3$ is 6H-dibenzo[b,d]pyranyl which may have suitable substituents(s),

or a salt thereof,

which comprises,

(1) reacting a compound of the formula :



wherein R^1, R^2, A, Q, X, and Y are each as defined above, and

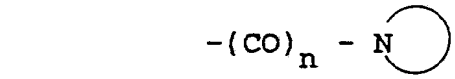
Z^1 is $-O-$, $-S-$ or $-\overset{R^6_a}{\underset{|}{N}}-$

in which R^6_a is lower alkyl or amino protective group,

or a salt thereof, with a compound of the formula :

$W^1-R^3_a$

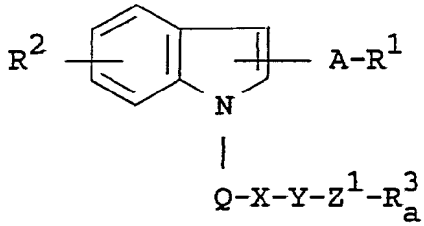
wherein R_a^3 is ar(lower)alkyl which may have suitable substituent(s) or a group of the formula :



in which  and n are each as defined above, and

W^1 is acid residue,

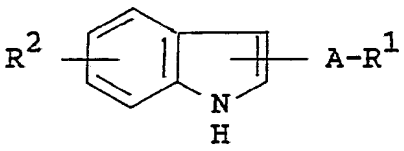
or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R_a^3, A, Q, X, Y and Z^1 are each as defined above,

or a salt thereof, or

(2) reacting a compound of the formula :



wherein R^1, R^2 and A are each as defined above,

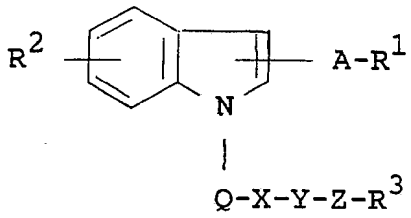
or a salt thereof, with a compound of the formula :

$$W^2\text{-}Q\text{-}X\text{-}Y\text{-}Z\text{-}R^3$$

wherein R^1, R^3, Q, X, Y, Z and A are each as defined above, and

W^2 is acid residue,

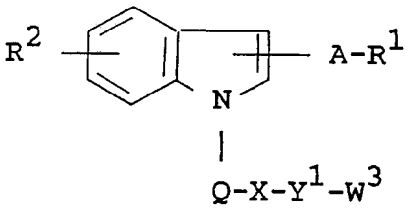
or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R^3, A, Q, X, Y and Z are each as defined above,

or a salt thereof, or

(3) reacting a compound of the formula :



wherein R^1, R^2, A, Q and X are each as defined above,

W^3 is acid residue, and

Y^1 is lower alkylene,

or a salt thereof, with a compound of the formula :

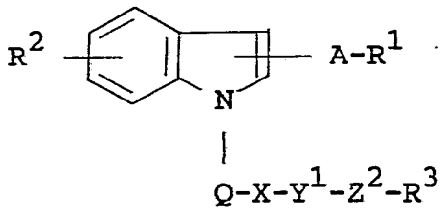
$$H\text{-}Z^2\text{-}R^3$$

wherein R^3 is as defined above, and

Z^2 is -O- or $-N(R^6)-$

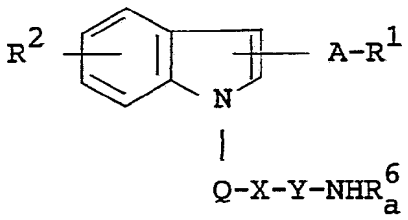
in which R^6 is as defined above,

or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R^3, A, Q, X, Y^1 and Z^2 are each as defined above,
or a salt thereof, or

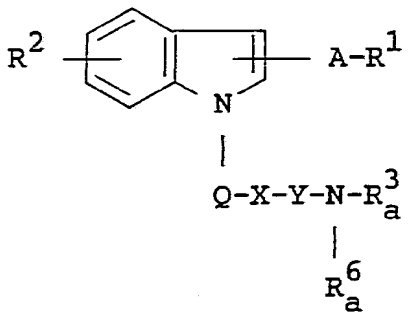
(4) reacting a compound of the formula :



wherein R^1, R^2, R^6_a, A, Q, X and Y are each as defined above,
or a salt thereof, with a compound of the formula :

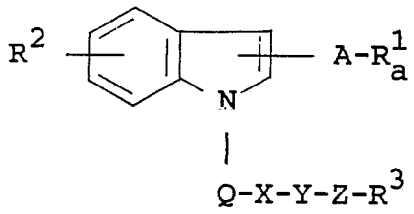
$$W^1 - R^3_a$$

wherein R^3_a and W^1 are each as defined above,
or a salt thereof, to give a compound of the formula:

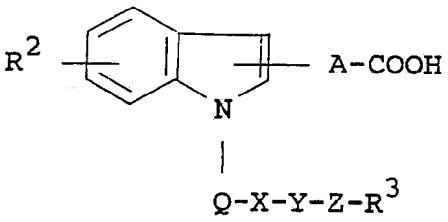


wherein R^1, R^2, R^3_a, R^6_a, A, Q, X and Y are each as defined above,
or a salt thereof, or

(5) subjecting a compound of the formula :

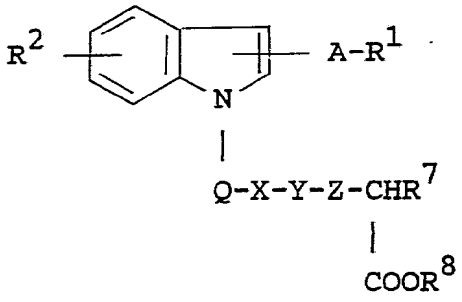


wherein R^2, R^3, A, Q, X, Y and Z are each as defined above, and
R^1_a is protected carboxy,
or a salt thereof, to elimination reaction of the carboxy protective group, to give a compound of the formula :

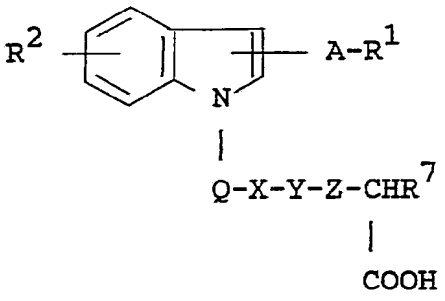


wherein R^2, R^3, A, Q, X, Y and Z are each as defined above,
or a salt thereof, or

(6) subjecting a compound of the formula :

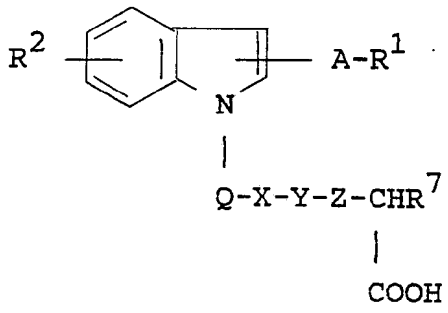


wherein R^1, R^2, A, Q, X, Y and Z are each as defined above,
R^7 is aryl which may have suitable substituent(s), and
R^8 is carboxy protective group,
or a salt thereof, to elimination reaction of the carboxy protective group, to give a compound of the formula :



wherein R^1, R^2, R^7, A, Q, X, Y and Z are each as defined above,
or a salt thereof, or

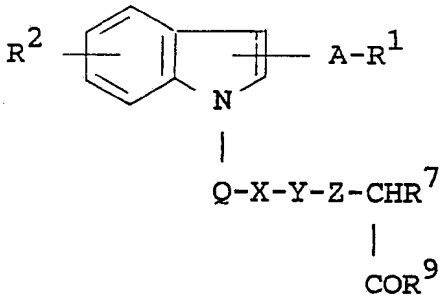
(7) reacting a compound of the formula :



wherein R^1, R^2, R^7, A, Q, X, Y and Z are each as defined above,
or its reactive derivative at the carboxy group or a salt thereof, with a compound of the formula :

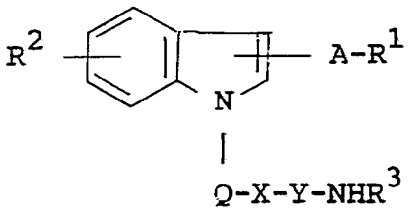
$$H\text{-}R^9$$

wherein R^9 is amino which may have suitable substituent(s),
or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula:



wherein R^1, R^2, R^7, R^9, A, Q, X, Y and Z are each as defined above,
or a salt thereof, or

(8) reacting a compound of the formula :



wherein R^1, R^2, R^3, A, Q, X and Y are each as defined above,

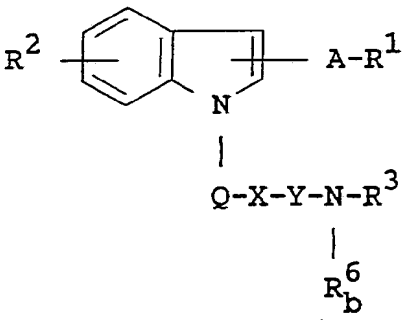
or a salt thereof, with a compound of the formula :

$$W^4\text{-}R_b^6$$

wherein R_b^6 is lower alkyl, ar(lower)alkyl which may have suitable substituent(s) or amino protective group, and

W^4 is acid residue,

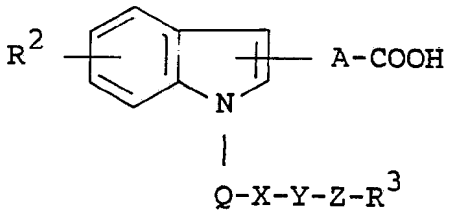
or a salt thereof, to give a compound of the formula:



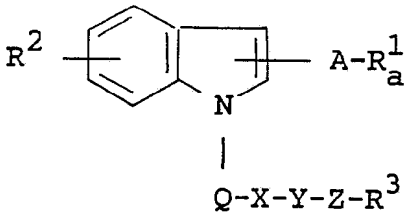
wherein R^1, R^2, R^3, R_b^6, A, Q, X and Y are each as defined above,

or a salt thereof, or

(9) subjecting a compound of the formula :



wherein R^2, R^3, A, Q, X, Y and Z are each as defined above,
or a salt thereof, to introduction of the carboxy protective group, to give a compound of the formula :



wherein R^1_a, R^2, R^3, A, Q, X, Y and Z are each as defined above,
or a salt thereof.

5. A pharmaceutical composition comprising a compound of claim 1 or pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

6. A method for treating or preventing testosteron 5α-reductase-mediated diseases, which comprises administering a compound of claim 1 or pharmaceutically acceptable salt thereof to human being or animals.

7. Use of a compound of claim 1 or pharmaceutically acceptable salt thereof as a medicament.

8. Use of compound of claim 1 or pharmaceutically acceptable salt thereof as a testosteron 5α-reductase inhibitor.

9. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or pharmaceutically acceptable salt thereof with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 92/00981

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 209/26 A 61 K 31/405 C 07 D 405/06

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 209/00 C 07 D 405/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
P,X	WO,A,9113060 (FUJISAWA PHARMACEUTICAL CO., LTD) 5 September 1991, see complete document	1,5,8

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21-09-1992	21. 10. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Markus Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 92/00981

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 6 is directed is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has be en carried out and based on the alleged effects of the compound/composition

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9200981 SA 62818

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/10/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 9113060	05-09-91	AU-A- 7257991	18-09-91
		CN-A- 1054250	04-09-91